IN THE NAME OF GOD

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Review

Review

The Role of Iodine for Thyroid Function in Lactating Women and Infants

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ESSENTIAL POINTS

- Iodine nutrition is a key determinant of thyroid function: Both iodine **deficiency** and **excess** may impair thyroid hormone production and thereby affect metabolism, growth, and development.
- The physiological iodine requirement is high in lactating women, infants, and toddlers, but current dietary intake recommendations are poorly defined, vary substantially between countries and need to be harmonized.

- Human milk is the main source of iodine for infants, and BMIC strongly depends on the maternal iodine intake a few hours before breastfeeding.
- Iodine status is best assessed by BMIC in lactating women and UIC in infants and toddlers, but the thresholds currently used to define optimal iodine nutrition in these groups are uncertain and should be revised using new scientific advances.

- Iodine status in lactating women, infants, and toddlers varies considerably worldwide: Mild iodine deficiency and excess iodine intake may be widespread, but quality data are limited and the impact on child development is uncertain.
- Salt iodization is the primary public health intervention to prevent iodine deficiency and provides sufficient dietary iodine to ensure adequate iodine nutrition in lactating women, breastfed infants and weaning infants.

- In populations with poor coverage of iodized salt and documented low iodine intake, iodine supplementation in lactating women and dietary interventions for toddlers may be required.

Table 1. Biomarkers of population iodine status in infants, toddlers, and lactating women

Biomarker	Population group	Specimen	Analytical method	Advantages	Disadvantages	Threshold defining iodine sufficiency in populations
UIC	Infants/ toddlers lactating women	Spot urine Infant samples can be collected using urine pads or urine bags	Spectrophotometric (Sandell-Kolthoff reaction) ICP-MS	Noninvasive Reflects recent iodine intake (within h) Assess intake from all dietary sources External quality control program in place (307)	High intraindividual and interindividual variability due to large variation in iodine intake and urine volume (249, 306) Large sample size needed(306) Not useful for individual assessment unless ≥ 10 repeated samples collected (306) UIC in lactating women should be assessed along with BMIC as fractional iodine excretion may vary in urine and breast milk (250)	Median UIC > 100 μg/L in lactating women and infants recommended by WHO (176), but evidence for this threshold in lactating women, infants, and toddlers is weak. Median UIC >200 μg/L likely more appropriate in infants (see Fig. 3) Criteria indicating deficient, optimal, and excessive iodine intake should be defined
BMIC	Lactating women	Spot breast milk	ICP-MS	Noninvasive Reflects recent iodine intake (within h)	High intraindividual variability due to large day-to-day variability in iodine intake Not reliable for individual assessment	Not yet adopted (21) Observational studies suggest median BMIC of between 100 and 200 μg/L indicate iodine sufficiency(18, 250) (Fig. 3)
Tg	Infants/ toddlers, lactating women	Serum or DBS	ELISA	Venopuncture Simple collection by finger or heel prick and storage on filter paper Small sample volume Reflects intermediate iodine status (wk to mo)	Values elevated at deficient and excessive iodine intakes and should be accompanied by UIC Wide interassay variation Affected by degradation when stored under hot and humid conditions (DBS)	Criteria indicating optimal iodine nutrition to be defined Assay specific reference ranges: to be defined for most assays (physiological decline during first mo of life must be considered)

Neonatal TSH	Neonates 2-5 d after birth	Serum or DBS	Various immunoassays	Collection by heel prick and storage on DBS is simple International reference range available Measures thyroid function at a particularly susceptible age	Should be taken at least 48 h after birth to avoid TSH surge Primarily reflects exposure to iodine deficiency during pregnancy Reflects population risk of moderate-to-severe iodine, but insensitive to mild iodine deficiency May be confounded by use of iodine-containing antiseptics at birth	Prevalence < 3% of values > 5 mIU/L indicates iodine sufficiency (176), but threshold < 5 mIU/L may be more sensitive to detect mild iodine deficiency

Abbreviations: BMIC, breast milk iodine concentration; DBS, dried blood spots; ELISA, enzyme-linked immunosorbent assay; ICP-MS, inductively coupled plasma mass spectrometry; Tg, thyroglobulin; TSH, thyrotropin; UIC, urinary iodine concentration.

- Maternal and infant nutrition determines child development and later adult health. For the first 6 months of life, exclusive breastfeeding is the norm for optimal infant nutrition. The nutritional composition of human milk typically depends on the maternal dietary intake and nutritional status, but the association between **maternal nutrient intake**, human **milk composition**, and **nutrient adequacy in infants** is still poorly understood. Iodine is an essential component of thyroid hormones and a particularly critical nutrient for child development.

- Poor iodine nutrition may impair thyroid hormone synthesis and thereby affect physical, neurological, and intellectual development .
- The importance of adequate iodine intake during pregnancy is well recognized, but the role of iodine for the prevention of thyroid disorders during lactation and infancy has only recently gained scientific attention.
- Iodine intake has improved remarkably in the general population over the past decades thanks to **salt iodization** but reports suggest lactating women, infants, and toddlers remain at risk of iodine deficiency .

- International health agencies and medical expert associations acknowledge iodine deficiency during lactation and infancy as a risk factor for
  - thyroid disease
  - compromised infant development

and recommend targeted interventions to achieve optimal iodine nutrition.

- We describe the association between maternal iodine status, the composition of human milk, and the role of breast milk for optimal iodine nutrition in infants and toddlers.
- We discuss dietary iodine requirements, iodine status biomarkers, and public health strategies to prevent iodine deficiency.
- We provide a critical review of previous findings from experimental and epidemiological data and highlight remaining knowledge gaps.

Thyroid Function and Thyroid Disorders

Normal Physiology

- Dietary iodine is absorbed in the gastrointestinal tract, enters the systemic circulation, and is taken up into the thyroid cells via the sodium (Na^+) and iodide (I^-) symporter (NIS).
- I^- is oxidized in the thyroid gland by thyroid peroxidase (TPO) and covalently bound to the glycoprotein thyroglobulin (Tg) to form thyroxine (T4) and small amounts of 3,5,3′-triiodothyronine (T3).
- The biosynthesis and release of thyroid hormones to the circulation is controlled by the hypothalamic-pituitary-thyroid (HPT) axis via TSH in a negative feedback loop.
- TSH binds to the TSH receptor and induces the expression of Tg

- Thyroid hormone synthesis is tightly controlled, and the thyroid gland uses several specific mechanisms to ensure adequate hormonogenesis , likely as a result of the low availability of iodine throughout evolution .
- The thyroid gland efficiently stores iodine bound to Tg and this reserve may be used during periods of low intake.
- In peripheral tissues, T4 is converted to the metabolically active form T3 via deiodinase enzymes

- T3 binds to nuclear thyroid hormone receptors and regulates gene expression of a wide range of genes controlling including

❑ Metabolism

❑ Growth

❑ neurologic functions.

The roles of T3 on brain and neurocognitive development involve

✓ neuronal proliferation

✓ Migration

✓ glial differentiation

✓ myelination of the central nervous system.

T4 may also act directly on target tissues, although to a lesser extent than T3.

- The fetal thyroid gland starts producing thyroid hormone in the second trimester (~ 20 weeks), but the mother’s T4 contribution is still crucial.
- Fetal serum T4 levels gradually increase until birth.
- The placenta takes up iodine from the maternal circulation and serves as an iodine reservoir to maintain fetal iodine status and adequate thyroid hormone production .

- The HPT axis is fully mature first at term or in the early neonatal period.
- Immediately after delivery (30-60 minutes), serum TSH sharply rises to 60 to 80 mIU/mL as an adaptation to extrauterine life and then rapidly falls back to stable levels 3 to 5 days after birth.
- Placental iodine content has been negatively associated with TSH levels short after delivery .
- This physiological TSH surge stimulates the T4 and T3 production in the newborn. Serum T4 and T3 concentrations peak at 24 hours after birth, followed by a gradual decline to reach more stable concentrations around 5 to 7 days post partum.

- The decrease continues during infancy and childhood but at a slower rate.
- The turnover of T4 during infancy is high, and infants produce 3 times more T4 than adults per kg body weight (5-6 µg/kg/day in infants vs 1.5 µg/kg/day in adults) .
- Paradoxically, infants are born with minimal iodine stores (~ 300 µg) that last only a few days.
- Therefore, iodine must be supplied by breast milk (or infant formula) to maintain the physiological high T4 production rate.

Thyroid Dysfunction

Lactating women

- Abnormal thyroid function is common during the postpartum period and the incidence of both hypothyroidism and hyperthyroidism increase markedly compared to before and during pregnancy.
- Thyroid dysfunction detected during the first year after birth in women with no previous history of thyroid disease is generally classified as postpartum thyroiditis, except if the diagnosis is Graves disease.

- Postpartum thyroiditis is an inflammatory subclinical autoimmune thyroid disorder associated with postpartum immune rebound as well as the presence of TPO antibodies during pregnancy.
- Postpartum autoimmune thyroiditis typically occurs 1 to 4 months after delivery with a prevalence of 5% and often develops from a previous subclinical thyroiditis that is exacerbated after delivery.
- In the classic form, transient thyrotoxicosis is followed by transient hypothyroidism returning to euthyroidism by the end of the initial postpartum year.
- Inflammatory processes in the thyroid gland result in release of T4 and T3 from the follicular cells, and synthesis of the thyroid hormones resumes when the inflammation subside

- Iodine deficiency is a well-recognized risk factor for thyroid disorders in adults .
- The incidence of postpartum thyroiditis has not directly been demonstrated to be associated with iodine status.
- Some studies, but not all, observed an increased risk for TPO antibody positivity in iodine excess ,which in turn is associated with postpartum thyroiditis.
- Three small randomized studies have examined the effects of prenatal iodine supplement on postpartum thyroiditis, but none of the studies observed a difference in frequency or severity of the condition.

- A randomized controlled trial (RCT) of iodine supplementation (200 μg/day) to pregnant women in 2 mildly iodine-deficient populations observed no differences in

- maternal thyroid function tests
- thyroid volume
- thyroid antibodies

between groups during pregnancy or at 6 weeks post partum. Adequately powered studies are needed to exclude iodine deficiency as a risk factor for postpartum thyroiditis

- A recent study in women with pregestational Hashimoto thyroiditis suggests that maternal thyroid status in early pregnancy predicts postpartum thyroiditis and that **euthyroidism** is associated with a **higher rate** of **postpartum thyroiditis** than hypothyroidism.
- Women at particular risk of postpartum thyroiditis may be screened, but universal thyroid function screening post partum is not recommended

Infants

- Low circulating levels of thyroid hormones lead to hypothyroidism, which may be present in utero, at birth(congenital hypothyroidism)
- Or develop later in life (acquired hypothyroidism).
- Infants and children diagnosed with overt hypothyroidism (high TSH and low T4) are at increased risk of

❖ **cognitive deficits**

❖ **metabolic abnormalities**

❖ **impairments in growth**

❖ **delayed skeletal maturation**

- Congenital hypothyroidism (TSH ≥ 20 mIU/L) due to thyroid hormone deficiency at the end of pregnancy and/or early infancy is a common cause of intellectual impairment, with an incidence of approximately 1 in 2000 to 3000 newborns in populations with adequate or mildly deficient iodine intake.

It can be caused by

- i)disorders of thyroid gland development (dysembriogenesis or dysgenesis), accounting for 80% to 85% of cases
- ii) defects in any step of thyroid hormone synthesis, including mutations in genes involved in iodine handling, accounting for the remaining 15% to 20% cases.

- It should be noted that congenital hypothyroidism is unrelated to the physiological increase in infant TSH occurring immediately after delivery.
- Thanks to neonatal screening at 2 to 5 days after birth, infants with congenital hypothyroidism are identified and treated with LT4
- but 70% of infants worldwide are still not covered by screening programs.
- Mild or subclinical hypothyroidism (high TSH and normal T4) is increasingly being detected and diagnosed in newborns and infants, partly because of lower neonatal TSH-screening thresholds.

causes of subclinical hypothyroidism in pediatric populations:

- ✓ Iodine deficiency is likely but supporting data are lacking.
- ✓ maternal thyroid dysfunction
- ✓ gene defects (eg, TSH receptor mutations)
- ✓ genetic syndromes (eg, Down syndrome)
- ✓ autoimmune thyroid disease (ie, Hashimoto thyroiditis).

The consequences of mild or subclinical hypothyroidism on development in early infancy or childhood remain unclear ,but **neurocognitive deficits** in neonates are possible.

- In older infants or children, there is **no** clear evidence of growth restriction or neurocognitive impairments, but **subtle cardiovascular abnormalities** have been documented.
- Infants identified with subclinical hypothyroidism require close follow-up because elevated TSH may be transient in approximately half the cases.
- In contrast to adults, the risk of progression from subclinical hypothyroidism to overt thyroid dysfunction is generally **low** in children and **mildly elevated TSH** may **spontaneously** normalize over the **first year of life** if no underlying thyroid disorder is present

Hyperthyroidism characterized by :

- ❑ excessive thyroid hormone production
- ❑ growth acceleration
- ❑ advanced bone age
- ❑ Tachycardia
- ❑ mood disorders.

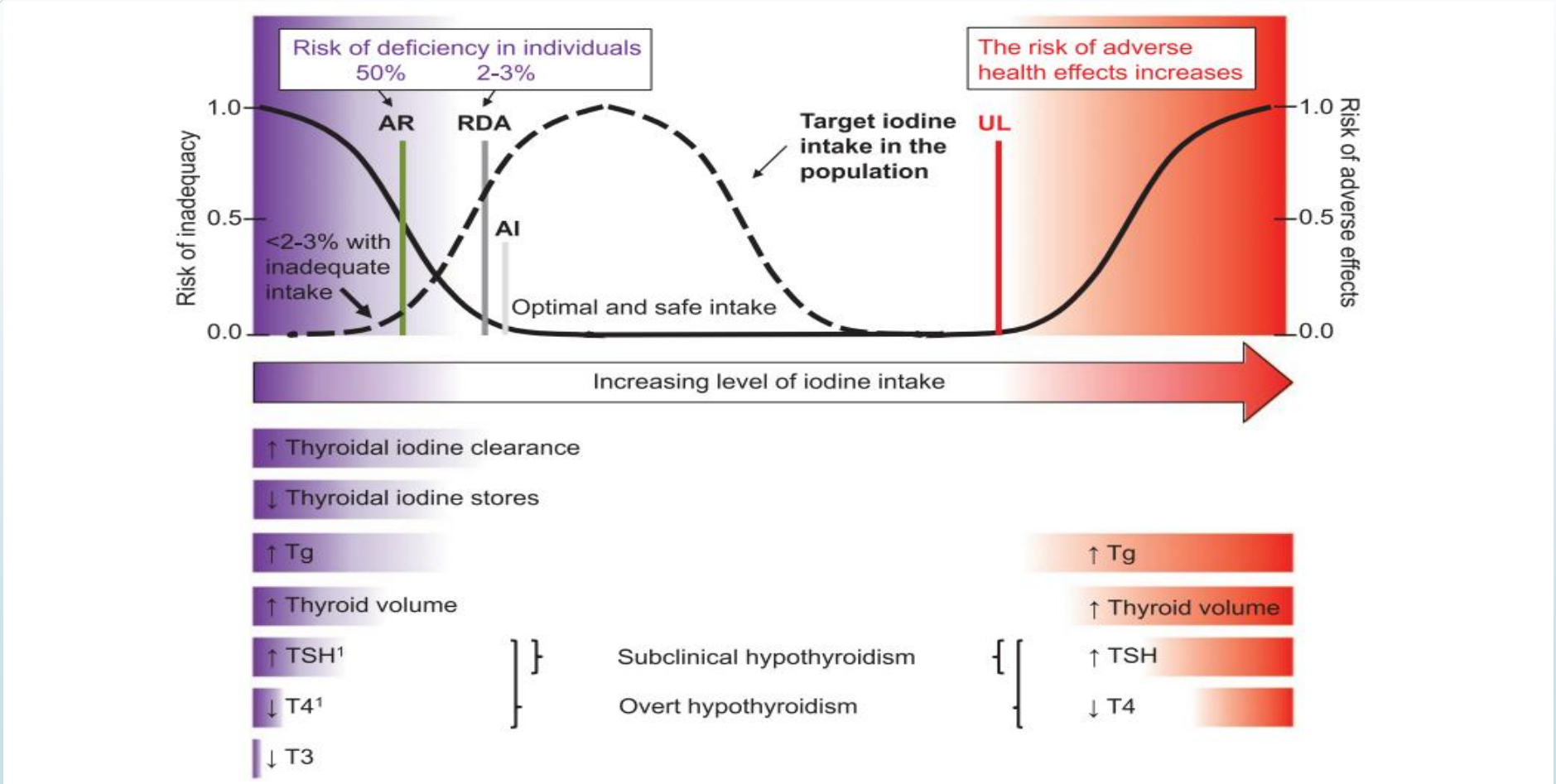
although serious, is rare in neonates and young children. Epidemiological data on thyroid function in pediatric are limited, apart from the initial screening at birth, and there is poor consensus on reference ranges for TSH and T4 during infancy and childhood. Clinical data suggest acquired overt pediatric thyroid disease is rare. Subclinical hypothyroidism appears to be less common in infants and children than in adults, but data are uncertain.

Health Consequences of Iodine Deficiency

Thyroid Function

- Iodine malnutrition can alter thyroid function and may cause thyroid disorders at any time throughout life.
- The association between iodine intake and thyroid function is U-shaped: Adverse effects are reported both at deficient and excessive intakes.
- The biological response to deficiency or excess occurs gradually, and the risk for thyroid dysfunction and subsequent functional consequences depends on the degree of iodine deficiency; the timing; duration of exposure.

Dietary reference intakes for iodine, risk of iodine malnutrition, and subsequent thyroid dysfunction



Severe iodine deficiency is associated with

- ✓ elevated Tg
- ✓ elevated TSH
- ✓ low T4
- ✓ whereas T3 often remains normal.
- ✓ The T3 /T4 ratio increases in serum
- ✓ the deiodination of T4 to T3 increases at the cellular level increase as adaptive mechanisms to minimize the risk of functional consequences due to iodine deficiency.

- Exposure to moderate iodine deficiency may slightly elevate TSH maintain serum T4 within normal or low normal ranges.
- Populations affected by **severe iodine deficiency** have
  - a high prevalence of goiter
  - overt hypothyroidism.

More than half of infants may be born with goiter.

- The incidence of congenital hypothyroidism can be as high as 1 in 10.
- The recall rate of **suspected** congenital hypothyroidism may be up to 10% (compared to 0.05%-0.2% in iodine-sufficient populations),
- but the rates of **confirmed** hypothyroidism vary .
- Correction of moderate-to-severe iodine deficiency in affected populations reduces the incidence of hypothyroidism.
- Congenital hypothyroidism due to exposure to severe iodine deficiency during pregnancy and infancy may persist into childhood.
- Moderate-to-severe iodine deficiency is also a risk factor for transient neonatal hypothyroidism (temporary high TSH& low T4) as well as for persistent subclinical hypothyroidism

Acquired transient neonatal hypothyroidism has been reported:

- neonates and infants of mothers with restrictive maternal diets(vegan diet)
- in infants under prolonged feeding of parenteral or enteral nutrition with low iodine concentrations.

- Mild iodine deficiency increases the thyroid activity, and elevated Tg concentrations are reported across all population groups.
- Although TSH and T4 overall remain within the normal range,
- mild iodine deficiency is a recognized risk factor for thyroid disorders in adults.

Are newborns and infants at higher risk for thyroid dysfunction due to iodine deficiency than adults ?

- Observational data in a moderate-to-severe iodine-deficient population suggest a higher prevalence of thyroid hypofunction in young infants than in their mothers, whereas other studies found no support.
- There is little evidence in mildly iodine-deficient populations.
- Considering the high rate of thyroid hormone synthesis and the low iodine stores, a sudden decline of the iodine intake would likely lead to a faster decrease in thyroid hormone concentration in infants than in their mothers.

Infant Mortality and Growth

- Moderate-to-severe iodine deficiency during pregnancy increases the risk for **stillbirth**, **miscarriage**, and **perinatal** and **infant mortality**, possibly through an increased risk of **low birthweight.**
- available data suggest no association between maternal UIC during pregnancy and anthropometric measures in newborns,
- whereas newborn TSH is negatively associated with birthweight.
- Iodine supplementation of severely iodine-deficient pregnant women improves mean birthweight, whereas no influence has been reported following iodine repletion of pregnant women exposed to mild to moderate iodine deficiency

- Iodine deficiency during infancy may impair growth, but adequately powered studies assessing the effects of iodine repletion on postnatal growth outcomes in term infants are lacking.
- Infant survival may also be affected by iodine status.
- A large cross-sectional study in Indonesia observed a higher prevalence of child malnutrition and mortality in neonates, infants, and children younger than 5 years among families using no or inadequately iodized salt compared to families consuming adequately iodized salt.

- An RCT of iodized oil (100 mg) given to 6-week-old infants in an iodine-deficient area of Indonesia observed lower infant mortality after the iodine intervention compared to placebo at age 4 months, but no difference was observed at age 6 months.

The studies are limited by:

- ❑ the small sample size used to assess mortality
- ❑ the lack of data on iodine status
- ❑ the lack of data on thyroid function in the mothers and infants.

Neurodevelopment

- Low thyroid hormone concentrations due to iodine deficiency may impair neurodevelopment.
- the effects of thyroid hormone inadequacy on the developing brain vary between stages of development and depend on the **degree**, **time** and **duration of exposure**.
- Iodine deficiency commonly occurs both in utero and after birth. The potential consequences on brain development may therefore be a result of combined prenatal and postnatal exposure.

- The most serious adverse effects of iodine deficiency on the brain are caused by exposure during fetal development. In populations affected by severe iodine deficiency, neonates may be born with:

- **neurological cretinism** due to maternal hypothyroxinemia during the first half of pregnancy. Infants are **typically euthyroid**.
- **Myxedematous cretinism** is also caused by severe iodine deficiency, possibly also in combination with dietary goitrogens (unprocessed cassava) or selenium deficiency, but results from fetal exposure during **late pregnancy and/or after birth**.

Myxedematous cretinism presents as

- severe hypothyroidism with similar clinical symptoms as in untreated congenital hypothyroidism,
- the degree of intellectual impairment is **less severe** than for neurological cretinism.

Severe maternal iodine deficiency leading to fetal hypothyroidism in utero may also cause other neurologic and cognitive deficits, including reduced IQ;

- Effects of mild iodine deficiency during pregnancy on brain and child development remain uncertain.
- A negative association between newborn TSH and cognitive development has been observed in iodine-deficient populations, but studies are small and data are inconclusive.

- A recent analysis of two pregnancy studies,
  - one in a borderline iodine-deficient setting
  - another in an iodine-sufficient setting

observed no association between neonatal TSH and childhood neurodevelopment at age 18 months.

- After birth, hypothyroidism exerts effects on **cerebellar development**, including language and verbal skills.
- little is known about the effects of iodine deficiency on neurological development during infancy.
- In an observational study in Chinese infants, breast milk iodine concentration (BMIC) in colostrum predicted motor development, but BMIC was not associated with cognition, language, or motor development in 18-month-old infants.

- A small RCT conducted in Iran reported higher cognitive scores in 36-month-old children whose mothers received 150 μg iodine/day compared to placebo during lactation, but no effect was observed in women who received 300 μg iodine/day.
- The study was conducted in an overall iodine-sufficient population, and observed no effect on language or motor development.
- Effects of iodine deficiency on cognitive functions during infancy are plausible, but evidence in mild-to-moderate iodine deficiency is lacking.

Health Consequences of Iodine Excess

- The physiological response to iodine excess is complex and depend on whether the exposure is acute or chronic, and if acute, if the habitual intake before exposure was deficient or adequate.
- In adults, the healthy thyroid is highly flexible and capable of adapting to high iodine intake, although excessive intake may still cause and/or aggravate hyperthyroidism, hypothyroidism, goiter, and thyroid autoimmunity.
- Elevated rates of thyroid dysfunction have been documented in lactating women exposed to iodine excess, although studies are small.

- **Acute excess** can cause a transient decrease in thyroid hormone production, a phenomenon known as the Wolff-Chaikoff effect. After adaptation, the gland “escapes” from this block and resumes thyroid hormone synthesis.
- The immature neonatal thyroid gland may be unable to escape from the acute Wolff-Chaikoff effect, possibly making the fetus and infant more susceptible to iodine induced hypothyroidism.
- Data in adults suggest that the susceptibility to excess iodine exposure may be higher in iodine-deficient populations compared to populations with otherwise adequate habitual iodine intake, but data in infants are limited

- Exposure to severe chronic iodine excess during pregnancy may cause fetal goiter that can obstruct the neonatal airway at delivery as well as congenital or transient hypothyroidism.
- In some individuals, chronic maternal intake just above the requirements may cause maternal hypothyroidism or isolated hypothyroxinemia. This could potentially affect cognitive development of the offspring, although data on the long-term effects are conflicting

- Excess maternal iodine intake and high BMIC may induce subclinical and clinical hypothyroidism in breastfed infants.
- The effects may be transient, but there is a risk of persistent thyroid dysfunction in both mothers and infants.
- Data in young infants and lactating mothers are mainly from case studies, and data in larger epidemiological studies is limited.
- Populations with chronic exposure to iodine intake above the requirements typically have elevated median Tg concentration, also consistently observed in observational studies of toddlers.

- Observational studies in infants exposed to excessive quantities of iodine in breast milk from lactating mothers receiving iodine therapy (4-100 mg/ day) for Graves disease have been conducted in Japan, where iodine intake is typically adequate to high.
- 12 percent of the infants had elevated TSH, indicating mild subclinical hypothyroidism
- and in most cases TSH normalized with cessation of the mother's iodine treatment.

- Another small study in neonates and infants exposed to high doses of iodine via contrast media observed transient elevation of TSH and drops in thyroid hormone concentrations, but no permanent thyroid dysfunction.
- The 3 studies suggest that the majority of infants exposed to excessive iodine intake may be able to maintain euthyroidism via initiation and then successfully escape from the WolffChaikoff effect, but larger studies are needed.

The susceptibility of exposure to excess iodine intake remains uncertain, but the effects likely depend on

- ❑ the level of excess
- ❑ and whether the exposure is acute or chronic.

In adults, morbidity due to excess iodine intake is usually transient. Concerns exist that excess iodine intake may trigger autoimmunity, but **thyroid antibodies** are **rare** in **children** and data in lactating women are limited.

The long-term effects of chronic excessive iodine intake on thyroid function, somatic growth, and development in infants and young children remain uncertain.

Dietary Reference Values for Iodine

- Nutrient adequacy in populations should be assessed based on the average requirement (AR), that is, the habitual intake estimated to meet the physiological requirement of half (50%) of healthy individuals of a specific life stage.
- The nutrient intake in a population is overall adequate when less than 2% to 3% of the populations have usual intakes below the AR.

- No AR has been defined for iodine in infants.The iodine reference intake for infants is instead defined as an **adequate intake** (**AI**) or as a **recommended daily allowance** (**RDA**).
- AI/RDAs are set at an average daily level that is assumed to be enough to meet the iodine requirements of nearly all (97.5%) healthy individuals. These reference intakes are used to assess intakes in individuals, not in populations.

Lactating Women

- The physiological requirement in a specific population group likely is the same across populations.
- International consensus on recommended iodine intakes in lactating women is lacking. Compared to before and during pregnancy, most bodies propose higher iodine intakes are needed during lactation to cover the physiological needs both of mother and infant.
- Reference values are based on median BMIC obtained from small cross-sectional studies, in many cases conducted in populations with low iodine intake.

- The US and Canada estimated the AR in lactating women at 209 µg/day. the RDA was set at 290 µg/day,
- twice that for women of reproductive age (150 µg/day)
- 1.3 times higher than for pregnant women (220 µg/day).

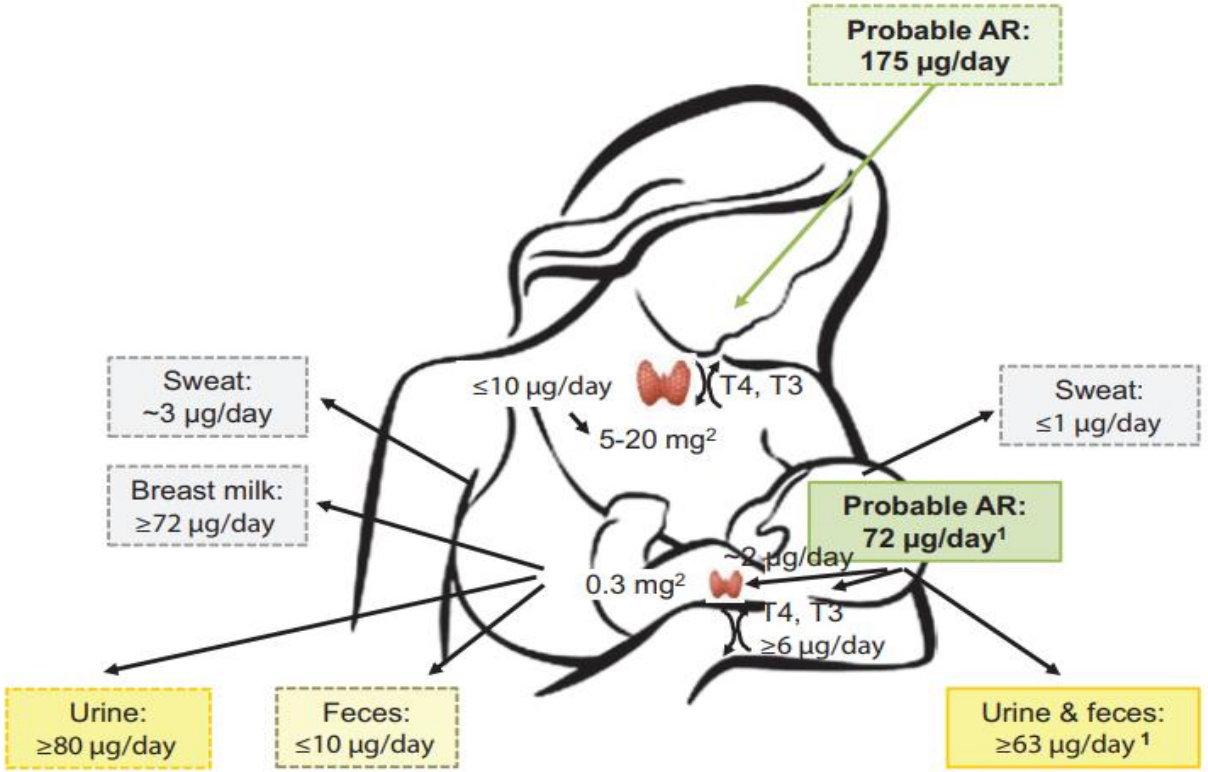
- The WHO recommends an iodine intake of 250 μg/day in lactating women, an additional 100 μg/day compared to nonpregnant, nonlactating adult women.
- The European Food Safety Authority (EFSA), the Nordic countries, Germany, Austria, and Switzerland are also presenting their intake recommendations as RNIs, ranging from 170 to 260 μg/day.

Infants

- The recommended intake of iodine for the first 6 months of life varies considerably between countries and bodies, ranging from 40 µg/day in Germany and Austria to 110 µg/day in the United States and Canada.
- The difference between countries reflects limited scientific data and different methodological approaches taken to set recommendations.
- As for many other nutrients, the recommended intake of iodine in this age group is typically based on the iodine concentration observed in human milk; this approach is problematic because the optimal BMIC has not been defined.

- A more reliable way to define dietary reference values is to estimate the intake level needed to achieve positive metabolic balance. This approach was used by the WHO and the recommended iodine intake was derived from a balance study conducted in a group of full-term infants in Belgium. Positive iodine balance was achieved at a minimum iodine intake of 15 μg/kg/day, corresponding to 90 μg/day at age 6 months (102 μg/day using current WHO weight-for age standards).
- However, this study was conducted at a time when the population in Belgium was iodine deficient and the estimated daily iodine requirement obtained in this study may be overestimated.

Schematic illustration of daily AR and iodine excretion pathways in lactating women and infants



	Body fluid	Excretion (µg/day)	Volume (L/day)	Iodine concentration (µg/L)	Population median iodine concentration (µg/L)
Infant	Urine	≥63[1]	0.5[3]	→ ≥125	→ >200
Mother	Urine	≥80	1.5	→ ≥50	→ >100
	Breastmilk	≥72	0.78[4]	→ ≥90	→ >>100

- Based on the study results obtained in iodine-sufficient infants, we propose that an AR of 72 μg/day and an RDA of 80 μg/day are required to maintain adequate iodine status during the first 6 months of life.

- Recent data from observational studies in 6- to 24-month-old toddlers show increased thyroid activity in populations with estimated average intakes of less than 50 µg/ day and more than 230 µg/day, suggesting a narrow optimal intake range at this age.

High Iodine Intake

- The tolerable upper level (UL) for iodine in lactating women is the same as for the general adult population, ranging from 600 µg/day to 1100 µg/day.
- It is based on the lowest observed adverse effect level of 1700 to 1800 µg/day.
- The Institute of Medicine applied an uncertainty factor of 1.5, bringing the UL to 1100 µg/day
- The EFSA used an uncertainty factor of 3 and set the UL at 600 µg/day.
- The WHO suggests an iodine intake of 1000 µg/ day is safe.
- The American Thyroid Association has taken a more stringent position and strongly recommends against habitual iodine intake exceeding 500 to 1100 µg/day while breastfeeding.

- A harmonized UL for iodine during lactation at 600 μg/day was recently proposed, but more data are needed to better define the potential risks of excessive iodine intakes in infants and lactating women.

Dietary Sources of Iodine

Lactating Women:

- The primary dietary source of iodine in the general population is iodized salt.
- Milk and dairy products are also important thanks to cattle feeds fortified with iodine and/or residues from iodine-containing sanitizers used for teat dipping and cleaning of equipment used in dairy production.
- Seafood and saltwater fish contain large amounts of iodine, but their contribution to overall iodine intake is generally limited because of infrequent consumption.
- The native iodine content in fruits, vegetables is low.

- Exclusively Breastfed Infantsn: rely on iodine provided by breast milk.
- Infants transitioning from breast milk to solid food may get iodine from a range of different dietary sources.

- Dietary iodine is primarily present as I– and is almost completely absorbed in the gastrointestinal tract.
- High bioavailability has been demonstrated in iodized salt, cow's milk, and infant formula (87%-92%).
- The chemical form or the composition of the diet is not known to affect the bioavailability.
- The bioavailability of iodine in breast milk has not specifically been investigated, but since iodine is mainly present as I – the bioavailability is likely comparable to that of infant formula and cow's milk .

Formula-fed Infants

- Infant formula used as a breast milk substitute must contain iodine to mimic breast milk.
- Most formulas are based on cow's milk containing iodine. The native iodine content is complemented with added potassium iodide (KI).
- The Codex standard for infant formula mandates a minimum iodine content of 10 μg/100 kcal and suggests an upper level of 60 μg/100 kcal.
- In the United States, infant formula must contain 5 to 75 μg/100 kcal.
- China 10.5 to 58.6 μg/100 kcal.
- European Union (EU) directives mandate a more narrow range of 15 to 29 μg/100 kcal.

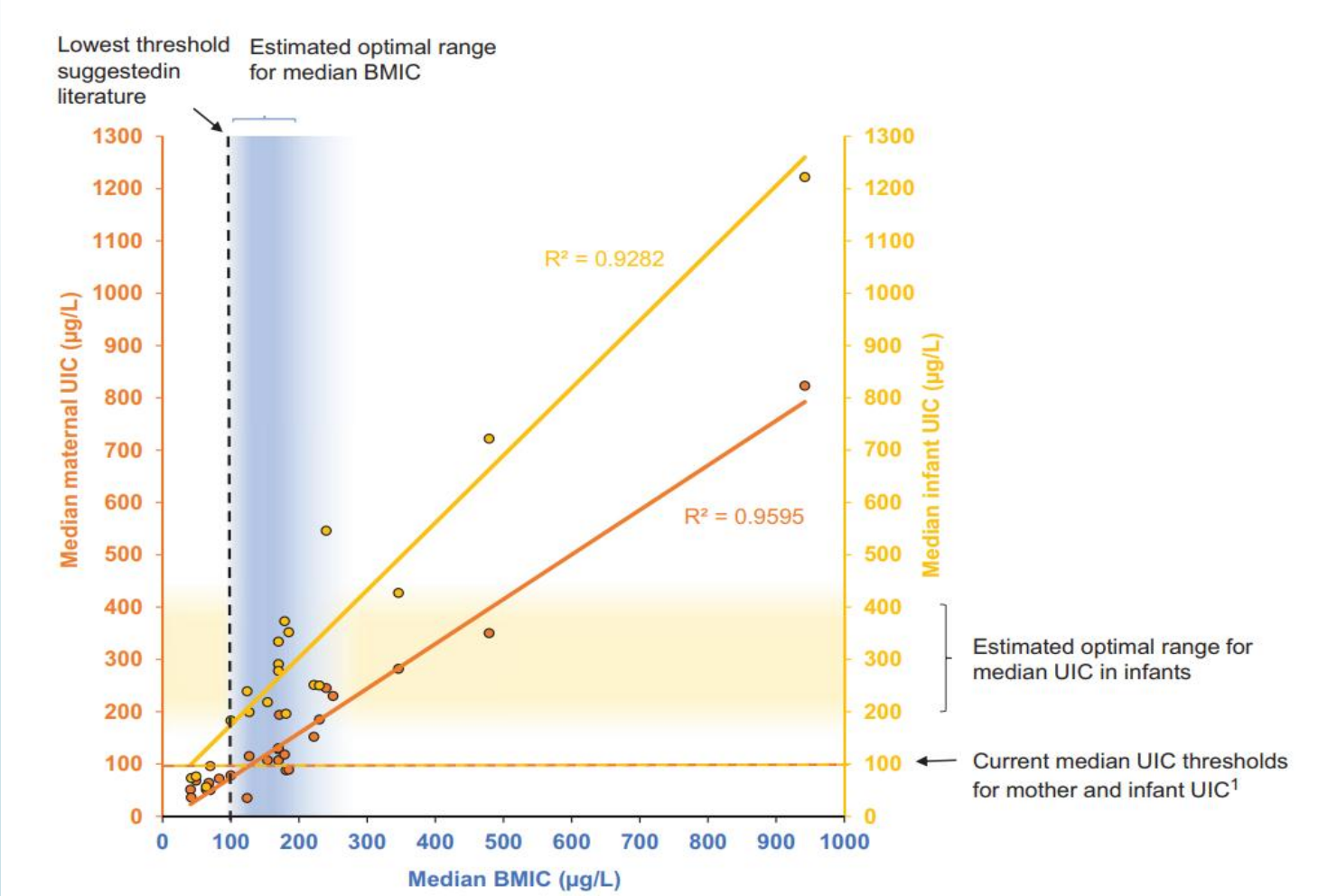
Epidemiology of Iodine Nutrition

- Iodine deficiency was historically widespread, but the implementation of salt iodization has remarkably improved the overall iodine intake in many countries.
- The number of countries worldwide classified as overall iodine deficient decreased from 54 to 21 between 2003 and 2021.
- Mild iodine deficiency may persist in population groups with high dietary iodine requirements.

- Data on iodine status in lactating women and infants are limited and most countries lack data.
- most studies have been conducted in selective locations using small sample sizes and few studies are nationally representative.
- The majority of studies assessed iodine status using UIC, and the interpretation is often misleading because of the uncertainty of the median UIC threshold.

- Median BMIC varies substantially across populations worldwide, ranging from as low as 20 μg/L to 1000 μg/L.
- The iodine status of exclusively breastfed infants is strongly determined by the maternal BMIC. BMIC and infant UIC are strongly correlated in single studies as well as in a compiled analysis.
- Iodine nutrition is adequate in lactating women and infants in populations with high coverage of iodized salt.
- the median BMIC typically ranges from 120 to 200 μg/L, corresponding to an average iodine intake in infants of 95 to 150 μg/day and median infant UIC of 200 to 400 μg/L.

Association between BMIC (blue) and maternal UIC (orange) and/or infant UIC (yellow) from cross-sectional studies conducted in lactating mothers and their breastfed infants.



- In populations exposed to moderate iodine deficiency, the median BMIC may be low at 20 to 50 µg/L and median UIC in infants as low as 20 µg/L.
- Studies conducted in formula-fed infants report adequate median UIC,but data are limited.
- Some studies report lower median UIC in formula-fed infants compared to breastfed infants, whereas other studies observe no difference.
- A prospective Iranian study of iodine-sufficient women observed higher median UIC in breastfed infants compared to formula-fed infants in mothers receiving supplemental iodine at 300 µg/day, but not at a supplemental dose of 150 µg/day or placebo.

Excess iodine intake may arise from consumption of

- ❑ over-iodized salt
- ❑ drinking water high in iodine
- ❑ milk from animals with high iodine consumption
- ❑ seaweed
- ❑ dietary supplements
- ❑ Topical disinfectants used at delivery
- ❑ certain iodine-containing pharmaceuticals
- ❑ contrast media are other potential sources of exposure.
- ➨ Mothers with acute or chronic excessive iodine intake excrete large amounts of iodine in breast milk.if the BMIC remains high at such levels, this may indicate chronic excessive maternal iodine intake.

- lactating women and infants likely meet their dietary requirements in settings with well-implemented salt iodization, but may be at risk of iodine deficiency if the coverage of iodized salt is poor or incomplete.

- The iodine intake in weaning infants and toddlers varies considerably worldwide. Cross-sectional studies report a 10-fold difference in median UIC between populations with the lowest and highest iodine intake.

The iodine intake at this age depends on several factors:

- 1) maternal iodine intake and subsequent BMIC
- 2) amount of breast milk consumed
- 3) type of complementary foods consumed
- 4) use of iodized salt in complementary foods and its iodine concentration;
- 5) consumption of cows' milk, follow-up infant formulas, or complementary foods fortified with iodine.

- Weaning infants typically have adequate iodine intake in populations where iodized salt is readily available and breastfeeding rates are high.
- Iodized salt covers toddlers indirectly through breast milk and directly through consumption of salt-containing complementary foods, despite recommendations to limit salt during the first year of life
- Studies conducted in populations covered by mandatory salt iodization report median UIC in 7- to 24-month-old infants ranging from 200 to 350 μg/L and normal Tg concentrations

- Studies in Gambia and Morocco at a time with poor availability of iodized salt, low BMIC, no widespread consumption of cow's milk or infant formula report low median UIC ranging from 50 to100 along with elevated Tg.
- A national study in Switzerland reported low BMIC at 50 μg/L and UIC of 100 μg/L both in 6- and 12-month-old infants. Only 57% of infants were breastfed at age 6 months and 18% at age 12 months. Compliance with pediatric recommendations to limit salt intake during the first year of life was high.

Iodine nutrition in toddlers may be complex as the dietary intake depends on

- maternal iodine status
- breastfeeding rates
- weaning practices

which vary considerably between populations. Data are limited, but the few available studies suggest that both deficient and high iodine intake may be more common than previously assumed.

Intervention Strategies to Prevent Iodine Deficiency

Salt Iodization: recommended iodine concentration in salt is 20 to 40 mg/kg. Scale-up of salt iodization programs around the world over the past decades has remarkably improved iodine nutrition.

- In this setting BMIC ranges: 120 to 200 μg/L , UIC in infants: 200 to 400 μg/L, suggesting iodine sufficiency.

Iodine Supplementation to Lactating Women:

- Daily iodine supplements are typically provided in the form of KI or iodate. Supplemental iodine appears rapidly in breast milk and the BMIC peaks at 6 hours after administration.
- In iodine-deficient populations with poor coverage of iodized salt, the WHO recommends daily iodine supplementation so that the total intake is 250 μg/day during pregnancy and lactation.
- Prenatal and postnatal iodine supplementation (150 μg/day) is also recommended by several national authorities and medical societies, regardless of the coverage of iodized salt.

- ✓ Observational studies in lactating women show higher BMIC in iodine supplement users compared to nonusers.
- ✓ Prospective studies examining the effect of postpartum iodine supplementation are limited.

To our knowledge 4 trials have been conducted in iodine deficient :

- ✓ Mulrine et al conducted a small RCT of iodine supplementation providing 75 μg/day, 150 μg/day, or placebo over 6 months to mildly to moderately deficient lactating women in New Zealand. BMIC remained low throughout the study, ranging from 24 to 70 μg/L, and no overall time-by-treatment effect was reported. Compared to placebo, BMIC was modestly higher in women consuming 75 μg/day and 150 μg/day, but no dose response was observed. Infant UIC remained low in all groups.

- Pedersen et al evaluated 200 μg daily iodine vs control from weeks 17 to 18 of pregnancy until 12 months after delivery in 54 women. Five days after delivery, BMIC and infant UIC were higher in mothers receiving iodine, although they were still low in both groups. Supplemented mothers maintained higher UIC and Tg during the postpartum period compared to nonsupplemented mothers, whereas TSH, T4 , T3 , and free T4 levels were unaltered.

- small prospective trial assessed iodine supplementation with daily doses of 50 or 200 μg during pregnancy, continuing to 6 months after delivery in mildly iodine deficient women in Italy.
- The urinary iodine excretion in pregnant women at enrollment was 74 μg/g creatinine and increased at 6 months post partum to 123 μg/g in the group receiving 50 μg/day and to 156 μg/g in the group receiving 200 μg/day.
- the study had no control group and did not measure BMIC. No group differences were observed for maternal thyroid volume, serum concentrations of Tg, TSH, free T4 , or free T3 .

- Another larger trial evaluated daily consumption of lipid-based nutrient supplements (LNS) containing 250 μg iodine or no iodine during pregnancy and lactation in moderately iodine-deficient women in Bangladesh.
- The geometric mean UIC in pregnant women at enrollment (13 weeks' gestation) was low at 50 μg/L and declined further in both groups at 36 weeks' gestation and 6 months post partum, with no difference between the groups.
- The efficacy of iodine supplementation in the postpartum period is difficult to evaluate in this study because BMIC and infant UIC were not measured.

- Two small studies evaluated iodine supplementation to lactating women with adequate iodine intakes. The first study compared iodine supplementation (225 μg/ day) to household distribution of iodized salt (30- 40 mg/kg of salt) over 6 months in lactating women in rural southern Ethiopia.
- The median BMIC at baseline was 150 μg/L. BMIC decreased in both groups over 6 months and infant UIC remained stable, but as expected no group differences were reported in BMIC, maternal UIC, or infant UIC.
- Most of the infants had normal T4 and all had TSH within the normal range

- A small RCT evaluated iodine supplementation of 150 μg/day, 300 μg/day, or placebo given to lactating women over 12 months in Iran, where iodized salt is widely available.
- The authors report an overall effect of both doses on BMIC and maternal UIC and a significant effect of infant UIC of the highest dose.
- However, the results are difficult to interpret because the groups differed at baseline. The iodine status in the placebo group remained iodine sufficient over the 12-month study.

- In summary, although dietary iodine supplementation during lactation likely improves BMIC in iodine-deficient populations, the evidence from RCTs is weak and the optimal dose remains uncertain.
- The few existing trials of daily iodine supplementation observed limited efficacy, but the studies were poorly powered, had no control group, did not measure BMIC, or were conducted in iodine-sufficient mothers.
- Only one study measured thyroid function in infants and none of the controlled studies evaluated long-term health gains of iodine repletion in infants. Thus, guidelines for postnatal iodine supplementation in iodine-deficient populations await the availability of well-designed efficacy studies that measure BMIC, infant iodine status, thyroid function, and functional outcomes of the infant.
- The data provide no support for targeted iodine supplementation to lactating mothers in settings where women are covered by a well working salt iodization program.

- Iodized oil is a slowly released iodine preparation that can be used as an alternative approach to daily iodine supplementation in severe iodine deficiency.
- It is typically administered on an annual basis as a large oral dose (400 mg to lactating women), but can also be injected intramuscularly.
- Supplementation with oral iodized oil is recommended in areas where iodized salt and complementary food fortified with iodine are unavailable and daily iodine supplementation is not feasible.

- The efficacy of oral iodized oil given to lactating women or infants was recently evaluated in a population of moderate to severe iodine deficiency in Morocco.
- Iodized oil was provided soon after delivery to mothers (400 mg, placebo to infants) or infants (100 mg, placebo to mothers).
- The study showed that administration of iodized oil is more beneficial when given to the mother than when given directly to infants.
- the BMIC of the supplemented mothers was significantly higher than that of the outhers at 3, 6, and 9 months, the improvement in BMIC was modest.
- The BMIC and infant UIC observed after iodized oil supplementation at 3, 6, and 9 months were 2 to 3 times lower than levels more recently reported in observational studies in iodine-sufficient populations.
- Indeed, contrary to the previous interpretation of the study results iodized oil failed to achieve longlasting optimal iodine nutrition in mothers and infants.

- Nevertheless, maternal iodine supplementation improved infant thyroid function, and the prevalence of hypothyroidism and hypothyroxinemia declined.
- A substudy showed that a large amount of iodine was excreted in the urine within the first few days after administration.
- However, a proportion of administered iodine was likely taken up by maternal fat deposits and metabolized back into the circulation at a slow rate and secreted into breast milk.
- The amount of circulating maternal iodine appears too low to substantially improve BMIC, but may still be sufficient to ensure euthyroidism in breastfed infants.

Dietary Interventions for Infants, Weaning Infants, and Toddlers

- During the first few months of life, infants should receive iodine through breast milk or infant formula. Dietary supplements aimed at this age group typically do not contain iodine.
- The WHO recommends infants aged 7 to 24 months in populations with poor coverage of iodized salt be given a daily dose of 90 µg iodine through fortified complementary foods.
- Daily iodine for this age group can be administered as crushable tables or iodine solutions, fortified infant formula or toddler milks, micronutrient powders (MNPs), or LNS.

- In subgroups with low breast milk and/or cow’s milk consumption, fortified commercial infant formulas or complementary food weaning infants may be at particular risk of iodine deficiency.
- iodine-fortified in-home fortification products to be sprinkled onto home-prepared complementary foods may be beneficial.

- Four prospective studies evaluated the impact of daily iodine on iodine status in toddlers both with low and adequate iodine intake
- A small study in iodine-deficient toddlers aged 12 to 20 months in New Zealand evaluated iodine-fortified toddler milk providing 90 μg/day compared to nonfortified milk (24 μg native iodine). The median UIC was 50 μg/L at baseline and increased to 91 μg/L in the iodine group after 20 weeks. In this population with overall low dietary iodine intake, the additional 90 μg/day was insufficient to achieve adequate iodine status.

- Another small observational prospective study over 44 weeks administered 90 µg/day as an iodine solution to mildly deficient infants aged 6 to 36 months in Belgium.The median UIC in infants at baseline was 101 µg/L and increased to 200 µg/L after 30 weeks and remained at this level thereafter, this study had no control group, limiting its interpretation.
- Another small study in 6- to 12-month-old Indonesian infants provided 60-µg iodine daily as a food-like crushable tablet over 6 months and compared it with weekly administration of 120-µg iodine, daily iron with no iodine, and placebo. The median UIC increased from 137 µg/L to 237 µg/L in the group receiving daily iodine. However, the UIC increased in all groups and at the end of the study, the change in UIC from baseline was comparable between the 4 groups. The study is limited by the small sample size, high breastfeeding rates, and the fact that one-third of the infants received infant formula containing iodine.

- Another study in 9-month-old infants in Burkina Faso evaluated the effect of 90 μg/day supplied in LNS, compared to no intervention. The median UIC was 222 μg/L at baseline, suggesting adequate iodine nutrition. After 9 months, the median UIC increased to 356 μg/L in the intervention group, but at age 18 months, no differences in UIC, TSH, T4 , or Tg were observed between the 2 groups. Adequately iodized salt was available in 95% of the households and all infants were partly breastfed at the beginning of the study, suggesting iodized salt likely provided sufficient iodine via breast milk.

- Taken together, in settings with adequate coverage of iodized salt and high breastfeeding rates, infants do not need additional iodine. Weaning infants and toddlers receiving homemade complementary foods with low native iodine content and no added salt or in settings with poor coverage of iodized salt likely benefit from consumption of complementary food products fortified with iodine or supplemental iodine. However, the evidence is obtained from small studies and the optimal daily dose of supplemental iodine in iodine-deficient populations as well as the timing of introduction remain uncertain. Well-designed and adequately powered controlled studies in iodine-deficient toddlers are warranted. Before including iodine in-home fortification products, the iodine status in the target group should be assessed and the iodine content should be adapted to avoid excess iodine intake.

- Two RCTs evaluated the effects of parenteral or enteral iodine of at least 30 μg/kg/day in preterm infants.
- The first study conducted in a small group of infants born before 33 weeks investigated the consumption of an enteral preterm infant formula providing iodine at 40 to 50 μg/kg/day vs 12 to 16 μg/kg/day until expected term at 40 weeks.
- No effects on thyroid function or growth were observed.

- The second study was conducted in a large group of preterms born before week 31 and evaluated the effect of iodine at 30 to 40 μg/kg/day vs placebo provided as parenteral or enteral nutrition until the equivalent of 34 weeks' gestation.
- The investigators found no group differences in Tg and T4 during the feeding period, apart from slightly higher TSH in the iodine group.
- At age 2 years, there were no differences in neurodevelopment and mortality between the 2 groups.
- The results were unexpected and the investigators hypothesize that the iodine requirement may be higher than 30 μg/ kg/day.However, the data are inconclusive and a lower iodine requirement is also possible.

- The intake recommendations for preterm infants should be based on the average dietary iodine requirements and harmonized between all feeding modes. However, the optimal intake range in preterm infants remains uncertain and carefully conducted balance studies in preterm infants are warranted to better define the daily needs and understand the etiology of hypothyroxinemia in preterm infants.

Conclusions

- Adequate iodine nutrition is essential for optimal thyroid function in lactating women, infants and toddlers.
- Moderate-to-severe iodine deficiency and iodine excess increase the risk for abnormal thyroid function, whereas adequate thyroid hormone production is typically maintained under mild iodine malnutrition.
- Elevated blood Tg concentration is the first measurable sign of mild iodine deficiency or excess.
- This is a physiological response indicating biological adaptation to prevent low hormone levels and functional consequences. However, data in infants and young children are limited.

- Iodine status is best assessed by BMIC in lactating women and UIC in infants and toddlers.
- Adequate iodine intake is indicated by a population median BMIC between 100 to 200 μg/L and median UIC >200 μg/L in infants and toddlers. Accumulated evidence suggests a linear association between BMIC and UIC in breastfed infants over a wide range of iodine intake levels.

At particular risk for iodine deficiency are

- 1) breastfed and weaning infants in countries with no or voluntary salt iodization at low coverage or fed by mothers on a restrictive diet;
- 2) toddlers receiving homemade complementary foods with low native iodine content and no added iodized salt;
- 3) preterm and term infants under prolonged feeding of parenteral or enteral nutrition.

- Salt iodization is the primary public health strategy to prevent iodine deficiency. Observational studies confirm that iodized salt provides enough dietary iodine to meet the high iodine requirements of lactating women, breastfed infants, and toddlers if all salt consumed is adequately iodized. However, if the coverage of iodized salt is poor and the dietary iodine intake is low, iodine supplementation in lactating women and targeted dietary interventions for toddlers may be required.

- Future well-designed and adequately powered studies assessing the association between iodine status and thyroid function in pediatric populations are needed to assess vulnerability to iodine malnutrition at both ends of the intake range. The impact of iodine deficiency repletion on infant thyroid function, infant growth, and neurocognitive development during the first 2 years of life should be addressed by studies conducted in regions of mild-to-moderate iodine deficiency, applying a holistic approach including mothers and infants.

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