Chapter 22

Efficacy and Safety of Iodine Fortification

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Chapter Outline

22.1 INTRODUCTION: THE IODINE DEFICIENCY DISORDERS

The spectrum of disorders caused by iodine deficiency (ID) are shown in Table 22.1 (World Health Organization, 2007; Zimmermann and Boelaert, 2015a). They all result from inadequate thyroid hormone production due to lack of sufficient dietary iodine, an essential component of thyroid hormone. Recommendations for iodine intake for different age groups are shown in Table 22.2.

22.1.1 Diffuse Goiter and Mutinodular Toxic Goiter

Thyroid enlargement (goiter) is the classic sign of ID. It is a physiologic adaptation to chronic ID. As iodine intake falls, secretion of thyroid-stimulating hormone (TSH) increases in an effort to maximize uptake of available iodine, and TSH stimulates thyroid hypertrophy and hyperplasia. Initially, goiters are characterized by diffuse, homogeneous enlargement, but over time, nodular goiter often develops. Thyroid nodules typically arise from somatic mutations and are of monoclonal origin (Kopp et al., 1994); the mutations appear to be more likely to result in nodules under the influence of a growth promoter, such as ID. ID is associated with a high occurrence of multinodular goiter, which can cause hyperthyroidism; this is mainly seen in women older than 50 years (Laurberg et al., 1991). In addition, large goiters are unattractive, can obstruct the trachea and esophagus, and may compress the recurrent laryngeal nerves and cause hoarseness.

22.1.2 Neurocognitive Impairment

Although goiter is the most visible effect of ID, the most serious adverse effect is damage to the developing brain. Maternal thyroxine (T4) crosses the placenta before onset of fetal thyroid function at 10−12 weeks and represents up to 20%−40% of T4 measured in cord blood at birth (Sack, 2003). Normal levels of thyroid hormones are required for neuronal migration and myelination of the fetal brain, and lack of iodine irreversibly impairs brain development (Morreale de Escobar et al., 2004). Severe ID during pregnancy increases risk for stillbirths, abortions, and congenital abnormalities (Pharoah et al., 1971; Dillon and Milliez, 2000; Cobra et al., 1997). Iodine treatment of pregnant women in areas of severe deficiency reduces fetal and perinatal mortality and improves motor and cognitive performance of the offspring (Zimmermann, 2012).

Severe ID in utero causes a condition characterized by gross mental retardation along with varying degrees of short stature, deaf mutism, and spasticity that is termed cretinism (World Health Organization, 2007; Eastman and Zimmermann, 2017). Two distinct types—neurological and myxedematous—have been described. The more common, neurologic cretinism, has specific neurologic deficits that include spastic quadriplegia with sparing of the distal extremities. The myxedematous form has the

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TABLE 22.1 The Iodine Deficiency Disorders, by Age Group (World Health Organization, 2007; Zimmermann and Boelaert, 2015a)

Physiological Groups	Health Consequences of Iodine Deficiency
All ages	Goiter, including toxic nodular goiter
	Increased occurrence of hypothyroidism in moderate-to-severe iodine deficiency; decreased occurrence of hypothyroidism in mild-to-moderate iodine deficiency
	Increased susceptibility of the thyroid gland to damage and thyroid cancer from iodine radioisotopes (e.g., from radioactive fallout)
Fetus	Abortion
	Stillbirth
	Congenital anomalies
	Perinatal mortality
Neonate	Infant mortality
	Endemic cretinism
Child and adolescent	Impaired mental function
	Delayed physical development
Adults	Impaired mental function
	Iodine-induced hyperthyroidism
	Overall, moderate-to-severe iodine deficiency causes subtle but widespread adverse effects in a population secondary to hypothyroidism, including decreased educability, apathy, and reduced work productivity, resulting in impaired social and economic development

TABLE 22.2 Recommendations for Iodine Intake (μg/day) by Age or Population Group

Age or Population Group[a]	US Institute of Medicine (2001)	Age or Population Group[b]	World Health Organization (2007)
Infants 0–12 months[c]	110–130	Children 0–5 years	90
Children 1–8 years	90	Children 6–12 years	120
Children 9–13 years	120		
Adults ≥ 14 years	150	Adults > 12 years	150
Pregnancy	220	Pregnancy	250
Lactation	290	Lactation	250

[a] *Recommended daily allowance.*
[b] *Recommended nutrient intake.*
[c] *Adequate intake.*

predominant finding of profound hypothyroidism, with thyroid atrophy and fibrosis. In areas of severe ID, cretinism can affect 5%–15% of the population. Effective iodine prophylaxis will eliminate the appearance of new cases of cretinism in previously iodine-deficient populations (Eastman and Zimmermann, 2017).

The potential adverse effects of mild-to-moderate ID during pregnancy are unclear (Pearce et al., 2016).

Maternal subclinical hypothyroidism (an increased TSH in the second trimester) and maternal hypothyroxinemia (a free T4 concentration <10 percentile at 12-week gestation) are associated with impaired mental and psychomotor development of the offspring (Pop et al., 1999; Haddow et al., 1999). However, in these studies, the maternal thyroid abnormalities were unlikely due to ID.

Although ID in utero impairs fetal growth and brain development, its postnatal effects on cognition are less clear. Cross-sectional studies of moderate-to-severely iodine-deficient children have generally reported impaired intellectual function and fine motor skills; a meta-analysis estimated that populations with chronic ID experience a mean reduction in IQ of approximately 12 points (Bleichrodt et al., 1987). However, observational studies are often confounded by other factors that affect child development.

Overall, ID produces subtle but widespread adverse effects in a population, including decreased educability, apathy, and reduced work productivity, resulting in impaired social and economic development. Because mild-to-moderate ID continues to affect much of the global population and can impair cognition in children, ID is a common cause of preventable mental retardation worldwide (Delange et al., 2002). The International Child Development Steering Group identified ID as one of four key global risk factors for impaired child development where the need for intervention is urgent (Walke et al., 2007).

22.2 EFFICACY OF IODIZED SALT: NATIONAL AND GLOBAL IODINE STATUS

Only a few countries, Switzerland, some of the Scandinavian countries, Australia, the United States, and Canada, were completely iodine sufficient before 1990. Since then, globally, the number of households using iodized salt has risen from <20% to >75%, dramatically reducing ID (Iodine Global Network, 2017). This effort has been spurred by a coalition of international organizations, including ICCIDD (now called the Iodine Global Network), WHO, the Micronutrient Initiative (now called Nutrition International), and UNICEF, working closely with national iodine deficiency disorders (IDD) control committees and the salt industry; this informal partnership was established after the World Summit for Children in 1990 (Iodine Global Network, 2017). It has been funded by Kiwanis International, several private foundations, and country aid programs.

The Iodine Global Network (IGN) Global Scorecard tracks global and national progress toward iodine sufficiency (Iodine Global Network, 2017). In 2017, based on recent national or subnational data, only 19 countries remain iodine deficient, 110 have optimal iodine intake, and 10 have excessive iodine intake (Fig. 22.1). In the United States and the United Kingdom, iodine intakes have fallen over the past two to three decades, likely because of decreased iodine intake from dairy products. Although school-aged children in the United States and the United Kingdom are iodine sufficient (Fig. 22.1), pregnant women in the United Kingdom and the United States are now mildly iodine deficient (Zimmermann et al., 2015c; Caldwell et al., 2013). Other countries, because of over iodized salt or high iodine in groundwater (e.g., Somalia), have excessive iodine intakes (Kassim et al., 2014). Vietnam and Cambodia, two countries in Southeast Asia with previously effective iodized salt programs, have experienced backsliding, and may have relapsed to ID (Iodine Global Network, 2017). These changes emphasize the importance of regular and systematic monitoring of iodine status in countries, to detect both low and excessive intakes of iodine.

In 2017, of the 19 countries that remain iodine deficient, all are classified as mild-to-moderately deficient, and none as severely deficient. Whether mild-to-moderate ID in children has adverse effects has long been debated. Two recent randomized, placebo controlled, double-blind intervention trials in mild-to-moderately deficient SAC have shown clear benefits of iodine on cognitive and motor function (Zimmermann et al., 2006a; Gordon et al., 2009). Moderately iodine-deficient 10−12 year-old children ($n = 310$) in Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo (Zimmermann et al., 2006a). Compared to placebo, iodine treatment significantly improved performance on tests of information processing, fine motor skills, and visual problem solving. The second placebo-controlled, double-blind trial was conducted in mildly iodine-deficient New Zealand SAC ($n = 184$) randomly assigned to receive 150 μg I daily or placebo for 28 weeks (Gordon et al., 2009). The overall cognitive score of the iodine-supplemented group was 0.19 SDs higher than that of the placebo group ($P = .011$). Data from cross-sectional studies on iodine intake and child growth are mixed, with some studies finding modest positive correlations (Zimmermann et al., 2007). In five Asian countries, household access to iodized salt was correlated with increased weight-for-age and mid-upper-arm circumference in infancy (Mason et al., 2002). In iodine-deficient children, impaired thyroid function and goiter are inversely correlated with insulin-like growth factor (IGF)-1 and insulin-like growth factor binding protein (IGFBP)-3 concentrations (Wan Nazaimoon et al., 1996). Controlled trials reported that iodine repletion increased IGF-1 and IGFBP-3 and improved somatic growth in children (Zimmermann et al., 2007).

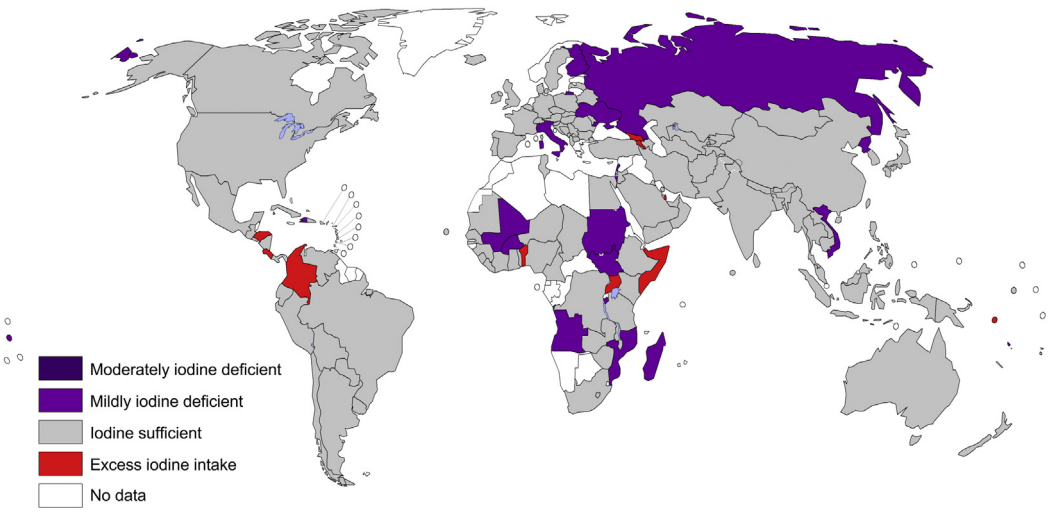

FIGURE 22.1 National iodine status in 2017, based on the median urinary iodine concentration in school-aged children (Iodine Global Network, 2017).

A recent systematic review (Bougma et al., 2013) examined the effects of iodine supplementation and/or status on mental development of children ≤5 years. Organized by study design, average effect sizes were: (1) 0.68 (two randomized controlled trials with iodine supplementation of mothers); (2) 0.46 (eight nonrandomized trials with iodine supplementation of mothers and/or infants); (3) 0.52 (nine prospective cohort studies stratified by mothers' iodine status); and (4) 0.54 (four cohort studies stratified by infants' iodine status). Overall, this translated into 6.9−10.2 lower IQ points in iodine-deficient children compared with iodine-replete children (Bougma et al., 2013). Thus, the available data, although limited, suggest ID of mild-to-moderate severity in SAC and in children ≤5 years has adverse effects on cognitive/motor performance and likely prevents children from attaining their full intellectual potential.

Observational studies have found that mild-to-moderate ID during pregnancy is associated with impaired cognitive development in the offspring (Bath et al., 2013). In Europe, several randomized controlled trials of iodine supplementation in mild-to-moderately iodine-deficient pregnant women have been done (Zimmermann, 2012). Iodine reduced maternal and newborn thyroid size, and, in some, decreased maternal thyrotropin (TSH). However, none of the trials showed an effect on maternal and newborn total or free thyroid hormone concentrations, probably the best surrogate marker for healthy fetal development and none measured long-term clinical outcomes, such as maternal goiter, thyroid autoimmunity, or child development (Zimmermann, 2012). A recent randomized placebo-controlled multicenter intervention trial that provided mildly iodine-deficient pregnant women iodine supplements did not find benefits on offspring development during infancy or 5 years of age (Gowachirapant et al., 2017).

Another systematic review by WHO on the use of iodized salt for preventing IDD summarized the efficacy of iodized salt (World Health Organization, 2014). Comparisons were made between the consumption of iodized salt and a placebo, noniodized salt, or no intervention. The review included 8 controlled trials, 20 quasiexperimental studies, 16 cohort observational studies, 42 multiple cross-sectional studies, and three studies with mixed designs. The participants included members of the general population of any age and sex. The results of this review showed that iodized salt has a remarkable benefits including reducing the risk of:

- Goiter (controlled trials risk ratio (RR) = 0.59 (95% CI, 0.36−0.95); cohort RR = 0.30 (95% CI = 0.23−0.41); multiple cross-sectional RR = 0.18 (95% CI = 0.14−0.22);
- Cretinism (multiple cross-sectional Peto odds ratio (OR) = 0.13 (95% CI, 0.08−0.20);
- Low IQ (quasiexperimental RR = 0.28 (95% CI, 0.21−0.36); multiple cross-sectional RR = 0.24 (95% CI, 0.07−0.82);
- ID, as indicated by low UI (multiple cross-sectional RR = 0.45 (95% CI, 0.33−0.60).

22.3 NUTRITIONAL GOITROGENS THAT INFLUENCE IODINE EFFICACY

Deficiencies of selenium, iron, and vitamin A exacerbate the effects of ID. Glutathione peroxidase and the deiodinases are selenium-dependent enzymes present in many tissues. In selenium deficiency, accumulated peroxides may

damage the thyroid, and deiodinase deficiency impairs thyroid hormone synthesis and these effects have been implicated in the etiology of myxedematous cretinism (Zimmermann and Köhrle, 2002). Iron deficiency reduces heme-dependent thyroperoxidase activity in the thyroid and impairs production of thyroid hormone, and goitrous children, iron deficiency anemia blunts the efficacy of iodine prophylaxis, while iron supplementation improves the efficacy of iodized oil and iodized salt (Hess et al., 2002; Zimmermann et al., 2003b). Vitamin A deficiency in iodine-deficient children increases TSH stimulation and risk for goiter through decreased vitamin A-mediated suppression of the pituitary TSHβ gene (Zimmermann et al., 2007).

22.4 ASSESSMENT OF IODINE STATUS IN POPULATIONS

Four methods are generally recommended for assessment of iodine nutrition in populations: urinary iodine concentration (UI), the goiter rate, serum TSH, and serum thyroglobulin (Tg) (World Health Organization, 2007). These indicators are complementary, in that UI is a sensitive indicator of recent iodine intake (days) and Tg shows an intermediate response (weeks to months), whereas changes in the goiter rate reflect long-term iodine nutrition (months to years).

Two methods are available for measuring goiter: neck inspection and palpation, and thyroid ultrasonography. Goiter surveys are usually done in school-age children (World Health Organization, 2007). Palpation of goiter in areas of mild ID has poor sensitivity and specificity; in such areas, measurement of thyroid volume by ultrasound is preferable for classifying goiter (World Health Organization, 2007). The total goiter rate is used to define severity using the following criteria: $<5\%$, iodine sufficiency; $5.0\%-19.9\%$, mild deficiency; $20.0\%-29.9\%$, moderate deficiency; and $>30\%$, severe deficiency (World Health Organization, 2007).

Because $>90\%$ of ingested iodine is excreted in the urine, UI is an excellent indicator of recent iodine intake (World Health Organization, 2007). UI can be expressed as a concentration (μg/L), in relationship to creatinine excretion (μg iodine/g creatinine), or as 24-hour excretion (μg/day). For national, school-based surveys of iodine nutrition, the median UI from a representative sample of spot urine collections from ≈ 1200 children (30 sampling clusters $\times$ 40 children/cluster) can be used to classify a population's iodine status (World Health Organization, 2007) (Table 22.3). However, the median UI is often misinterpreted. Individual iodine intakes, and, therefore, spot UI concentrations are highly variable from day-to-day (Andersen et al., 2007), and a common mistake is to assume that all subjects with a spot UI <100 μg/L are iodine deficient.

Tg is synthesized only in the thyroid, and is the most abundant intrathyroidal protein. In areas of endemic goiter, serum Tg increases due to greater thyroid cell mass and TSH stimulation (World Health Organization, 1994). In prospective studies, dried blood spot Tg has been shown to be a sensitive measure of iodine status and reflects improved thyroid function within several months after iodine repletion (Zimmermann et al., 2003a) and an international reference range and a reference standard is now available (Zimmermann et al., 2006b; World Health Organization, 2007). DBS-Tg may also be a sensitive biomarker of iodine nutrition in pregnant women (Stinca et al., 2017). In contrast, thyroid hormone concentrations are poor indicators of iodine status. In iodine-deficient populations, serum T3 increases or remains unchanged, and serum T4 usually decreases. However, these changes are often within the normal range, and the overlap with iodine-sufficient populations is large enough to make thyroid hormone levels an insensitive measure of iodine nutrition (World Health Organization, 2007).

22.5 THE SAFETY OF IODIZED SALT PROGRAMS AND THE EFFECTS OF IODINE EXCESS

Acute iodine poisoning caused by ingestion of many grams causes gastrointestinal irritation, abdominal pain, nausea, vomiting, and diarrhea, as well as acneiform skin eruptions, cardiovascular symptoms, and coma (Pennington, 1990). In areas of iodine sufficiency, healthy individuals are remarkably tolerant to iodine intakes up to 1 mg/day, as the thyroid is able to adjust to a wide range of intakes to regulate the synthesis and release of thyroid hormones (Chow et al., 1991). However, doses of iodine in the mg range may cause hypothyroidism in those with damaged thyroid glands because normal downregulation of iodine transport into the gland does not occur (Chow et al., 1991). Individuals with nodular goiter may also respond adversely to intakes less than 1 mg/day. In children, chronic intakes of ≥ 500 μg/day are associated with increased thyroid volume, an early sign of thyroid dysfunction (Zimmermann et al., 2005). European (European Commission, 2002) and US (Institute of Medicine, 2001) expert committees have recommended tolerable upper intake levels for iodine (Table 22.4), but caution that individuals with chronic ID may respond adversely to intakes lower than these. In monitoring populations consuming iodized salt, the WHO recommendations for the median UI that indicates excess iodine intake are shown in Table 22.3 (World Health Organization, 2007).

TABLE 22.3 Epidemiological Criteria for Assessing Iodine Nutrition in a Population Based on Median and/or Range of Urinary Iodine Concentrations (World Health Organization, 2007)

Median Urinary Iodine (μg/L)	Iodine Intake	Iodine Nutrition
School-aged children		
<20	Insufficient	Severe iodine deficiency
20–49	Insufficient	Moderate iodine deficiency
50–99	Insufficient	Mild iodine deficiency
100–199	Adequate	Optimal
200–299	More than adequate	Risk of iodine-induced hyperthyroidism in susceptible groups
>300	Excessive	Risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150	Insufficient	
150–249	Adequate	
250–499	More than adequate	
≥500	Excessive[a]	
Lactating women[b]		
<100	Insufficient	
≥100	Adequate	
Children less than 2 years old		
<100	Insufficient	
≥100	Adequate	

[a]*The term "excessive" means in excess of the amount required to prevent and control iodine deficiency.*
[b]*In lactating women, the figures for median urinary iodine are lower than the iodine requirements because of the iodine excreted in breast milk.*

TABLE 22.4 Tolerable Upper Intake Level for Iodine (μg/day)

Age Group	European Commission/Scientific Committee on Food (2002)	US Institute of Medicine (2001)
1–3 years	200	200
4–6 years	250	300
7–10 years	300	300
11–14 years	450	300
15–17 years	500	900
Adult	600	1100
Pregnant women >19 years	600	1100

An increase in iodine intake of populations with chronic ID may precipitate iodine-induced hyperthyroidism (IIH) (Delange et al., 1999). It has been reported in the introductory phase of several USI programs, including an outbreak in Zimbabwe and the DR Congo due to excessively iodized salt. IIH primarily affects older adults with long-standing nodular goiter whose iodine intake is rapidly increased (Delange et al., 1999). Thyrocytes in nodules often become insensitive to TSH control, and if iodine supply is suddenly increased, these autonomous nodules may overproduce thyroid hormone (Corvilain et al., 1998). IIH is nearly always transient and its incidence reverts to baseline after 1−10 years of intervention. However, it is dangerous when superimposed on underlying heart disease, and may be lethal (Delange et al., 1999). IIH prevention includes careful monitoring of salt iodine levels and training of regional health staff in IIH identification and treatment.

To investigate the effects of iodine intake on thyroid disorders in China (Teng et al., 2006; Yang et al., 2007), a 5-year, prospective community-based survey was done in three rural Chinese communities with mild-deficient, more than adequate (previously mild ID corrected by iodized salt), and excessive iodine intake from environmental sources; the median UI was 88, 214, and 634 μg/L, respectively. For the three communities, the cumulative incidence of hyperthyroidism was 1.4%, 0.9%, and 0.8%; of overt hypothyroidism, 0.2%, 0.5%, and 0.3%; of subclinical hypothyroidism, 0.2%, 2.6%, and 2.9%; and of autoimmune thyroiditis, 0.2%, 1.0%, and 1.3%, respectively. In most individuals, these later two disorders were not sustained. Among subjects with euthyroidism and antithyroid antibodies at baseline, the 5-year incidence of elevated serum thyrotropin levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. In all three communities, independent of iodine intake, either positive TPOAb (OR = 4.2 (95% CI 1.7−8.8) or goiter (OR = 3.1 (95% CI 1.4−6.8) in original healthy participants was associated with the occurrence of hyperthyroidism (Teng et al., 2006; Yang et al., 2007).

Denmark has documented the pattern of thyroid disease after careful introduction of iodized salt (Pedersen et al., 2006, 2007). New cases of overt hypothyroidism were identified in two areas of Denmark with previous moderate and mild ID, respectively (Aalborg, median UI = 45 μg/L; and Copenhagen, median UI = 61 μg/L), before and for the first 7 years after introduction of a national program of salt iodization. The overall incidence rate of hypothyroidism modestly increased during the study period: baseline, 38.3/100,000 per years; after salt iodization, 47.2/100,000 (versus baseline, RR = 1.23; 95% CI = 1.07−1.42). There was a geographic difference because hypothyroidism increased only in the area with previous moderate ID. The increase occurred in young and middle-aged adults. Similarly, new cases of overt hyperthyroidism in these two areas of Denmark before and for the first 6 years after iodine fortification were identified. The overall incidence rate of hyperthyroidism increased (baseline, 102.8/100,000 per year; after salt iodization 138.7/100,000 (P for trend $<.001$)). Hyperthyroidism increased in both sexes and in all age groups, but in contrast to IIH where most cases occur in older individuals, many of the new cases were observed in young subjects—the increase was highest in adults aged 20−39 years—and were presumably of autoimmune origin. A separate Danish report compared hyperthyroidism before and 4 years after salt iodization and also reported 50% lower rates of subclinical hyperthyroidism postiodization and a trend toward lower rates of overt hyperthyroidism, both independent of age (Vejbjerg et al., 2009).

The overall incidence of thyroid carcinoma in populations does not appear to be influenced by iodine intake (Zimmermann et al., 2015b). A study in Denmark suggested modest differences in iodine intake between regions did not affect thyroid cancer incidence (Sehestedt et al., 2006). A meta-analysis of four case-control studies of iodine intake and thyroid cancer found a significant inverse relationship between iodine and risk of thyroid cancer (Zimmermann et al., 2015b). Several studies have suggested the distribution of the subtypes of thyroid carcinoma is related to iodine intake; in areas of higher iodine intake, there appear to be fewer of the more aggressive follicular and anaplastic carcinomas, but more papillary carcinomas (Zimmermann et al., 2015b). When iodine prophylaxis is introduced in populations, there may be an increase in the ratio of papillary to follicular carcinoma, and this shift toward less malignant types of thyroid cancer, as well as a lower radiation dose to the thyroid in case of nuclear fallout, are benefits of the correction of mild-to-moderate ID (Zimmermann et al., 2015b).

Several reviews have examined the relationship between increases in iodine intake as a determinant of the pattern of thyroid diseases in populations (Laurberg et al., 2000; Zimmermann and Boelaert, 2015a). In summary, as a population moves from severe ID to mild ID and then to iodine sufficiency, there is a shift from excess hypothyroidism to excess hyperthyroidism, which is transient, and then a small shift back toward excess mild hypothyroidism. Severe ID causes more hypothyroidism because, despite an increase in thyroid activity to maximize iodine uptake and recycling, there is simply not enough iodine to maintain thyroid hormone production. In mild to moderate ID, the thyroid gland is able to compensate for deficient dietary intake by increasing thyroid activity and this maintains thyroid hormone production, but at a price: in some individuals, chronic stimulation of the thyroid will

lead to thyroid nodularity and autonomy (Zimmermann and Boelaert, 2015a). This increase in nodularity subsequently increases risk of hyperthyroidism if iodine intakes are raised by supplementation or fortification. However this is transient since iodine sufficiency normalizes thyroid activity resulting, in the long-term, in reduced nodularity and autonomy. The small increase in mild hypothyroidism that occurs with optimal or excessive iodine intakes may be linked to thyroid autoimmunity and may also transient, but more long-term studies are needed (Zimmermann and Boelaert, 2015a).

22.6 CONCLUSIONS

Concerns about potential small increases in iodine-induced thyroid disease should not delay or limit the implementation of iodine prophylaxis in iodine-deficient populations. Looking at the benefits versus the risks of iodine prophylaxis, it is clear that severe ID in pregnancy can cause hypothyroidism, poor pregnancy outcome, cretinism, and irreversible mental retardation. Mild-to-moderate ID in utero and in childhood results in less-severe learning disability, poor growth, and diffuse goiter. In adults, mild-to-moderate ID appears to be associated with higher rates of more aggressive subtypes of thyroid cancer, and increases risk for nontoxic and toxic nodular goiter and associated hyperthyroidism. On the other hand, increasing iodine intakes in deficient populations is not without risk, and more data is needed on the incidence of mild hypothyroidism and thyroid autoimmunity after salt iodization (Utiger, 2006; Zimmermann and Boelaert, 2015a). Clearly, programs of iodine prophylaxis need to carefully monitor for both ID and excess.

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