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Iodine Supplementation in Pregnancy and the Dilemma of Ambiguous Recommendations

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Key Words
Iodine supplement · Pregnancy · Urinary iodine concentration · Thyroid

Abstract
Iodine requirements are increased during pregnancy, predominantly caused by an increase in renal iodide clearance and in the use of iodine for thyroid hormone production. Because iodine deficiency (ID) in pregnancy may be associated with neurodevelopmental deficits in the offspring, a pertinent question is at what level of iodine intake pregnant women should be advised to take iodine-containing supplements. The consensus reached by the WHO/UNICEF/ICCIDD in 2007 was that pregnant women should not be recommended to take iodine-containing supplements if the population in general had been iodine sufficient for at least 2 years. However, guidance on this differs between scientific societies. This review discusses iodine supplementation in pregnancy. Based on current evidence, the recommendations given by WHO/UNICEF/ICCIDD in 2007 provide a valid guidance on the use of iodine supplements in pregnant women. Women living in a population with a median urinary iodine concentration (UIC) at or above 100 µg/l are not in need of iodine supplementation in pregnancy. On the other hand, if the population median UIC is below 100 µg/l, pregnant women should take iodine-containing supplements until the population in general has been iodine sufficient for at least 2 years by way of universal salt iodization.

Introduction

Iodine is required for thyroid hormone synthesis, and adequate production of thyroid hormones is essential for brain development [1]. In many populations the content of iodine in the diet tends to be below the recommended amount [2], and this may well lead to inadequate iodine intake among pregnant women because there is an increase in the need for iodine during pregnancy [3, 4]. Thus, in recent years there has been much focus on the potential need for individual intake of iodine-containing supplements among pregnant women.

In the present review, we discuss iodine supplementation in pregnant women. As part of this discussion, we touch upon the mechanisms of an increased need for iodine, the method used to evaluate iodine deficiency (ID) and the current recommendations on iodine supplementation in pregnant women, as well as the potential adverse consequences of inadequate or excessive iodine intake in pregnancy.

Definition of ID in a Population and in Pregnancy

The most authoritative guideline on how to assess iodine nutrition in a population (table 1) was published in 2007 by the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the International Council for Control of Iodine Deficiency Dis-

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orders [ICCIDD, currently the Iodine Global Network (IGN)] [5]. According to this guideline, a median urinary iodine concentration (UIC) in the range of 100–199 μg/l in a population of school-aged children and nonpregnant adults corresponds to adequate iodine nutrition, whereas a median below this specified range indicates that the population is iodine deficient. However, as depicted in table 1, this does not apply to pregnant women where the iodine concentration in the urine should be higher (150–249 μg/l) to indicate adequate iodine intake.

Table 1. Epidemiological criteria for assessing iodine nutrition based on median UIC

Median UIC, μg/l	Iodine intake	Iodine status
School-aged children (≥6 years)[a]		
<20	Insufficient	Severe ID
20–49	Insufficient	Moderate ID
50–99	Insufficient	Mild ID
100–199	Adequate	
200–299	Above requirements	
≥300	Excessive	
Pregnant women		
<150	Insufficient	
150–249	Adequate	
250–499	Above requirements	
≥500	Excessive	

Data are from [5].
[a] Applies to adults but not to pregnant and lactating women.

Mechanisms Leading to an Increased Need for Iodine during Pregnancy

A seminal study to illustrate in detail the increased need for iodine in pregnancy was performed by Aboul-Khair et al. [6] in 1964 (fig. 1). As illustrated, renal clearance of iodide increases considerably in pregnancy, presumably because of the pregnancy-associated increase in renal function, with a 75% higher renal plasma flow in mid-pregnancy and a 50% higher glomerular filtration rate from the late first trimester to the end of pregnancy [3]. If all other factors related to iodine metabolism were unaltered, such an increase in renal iodide clearance would lead to a new steady state, where urinary iodine excretion would be unaltered and would reflect iodine intake, but the plasma inorganic iodide (PII) concentration would be lower. The lower PII would increase the activity of the NIS (sodium-iodide supporter) in the thyroid gland via thyroid autoregulation, with a compensatory increase in thyroid iodide clearance to keep thyroid absolute iodide uptake (AIU) unaltered for thyroid hormone production [3].

However, as illustrated in the study by Aboul-Khair et al. [6] (fig. 1), AIU is not unaltered in pregnancy; it is about 50% higher than in nonpregnant controls. This high AIU corresponds to the 50% increase in thyroid hormone production starting in early pregnancy [7]. The major mechanism for the pregnancy-associated early increase in thyroid hormone production is the high levels of hCG (human chorionic gonadotropin) in early pregnancy, which stimulates the thyroid gland to an increased production of thyroid hormone and counteracts the very high levels and activity of the enzyme iodothyronine deiodinase type 3 in the utero-placenta unit, which inactivates T_4 and T_3 [8–10]. Thus, even if the metabolism of thyroid hormone increases considerably, there is a reduction of serum thyroid-stimulating hormone (TSH) in early pregnancy. The change in thyroid hormone metabolism in early pregnancy is illustrated by a shift in the balance between serum rT_3 and T_3 in maternal circulation from early pregnancy [11, 12].

The increase in renal iodide clearance and the increase in thyroid hormone production seem to be the major causes for the increase in the need for iodine during pregnancy, whereas other contributing factors, such as iodine accumulation in the placenta (15–30 μg during the entire pregnancy [13]) and in the fetus (100–300 μg, mainly in the thyroid gland [14, 15]), the increase in the distribution volume of iodide and thyroid hormones in pregnancy, and a gradual 50% increase in protein-bound T_4 and T_3 in the blood, are quantitatively much less important and only correspond to a net iodine accumulation of a few micrograms of iodine per day, as described in more detail previously [3].

Methods to Evaluate ID in Pregnant Women

Various methods may be used to assess iodine status in pregnant women, but the most commonly used and widely accepted is to estimate median UIC in 'a representative sample' [5]. On the other hand, sparse guidance exists on the selection of 'a representative sample' of pregnant women. It would often be convenient to collect urine samples from pregnant women when the women are visiting a clinic for maternity consultation or for obstetric ultrasound. However, it is important to be aware that a change in diet, including a change in fluid intake, may

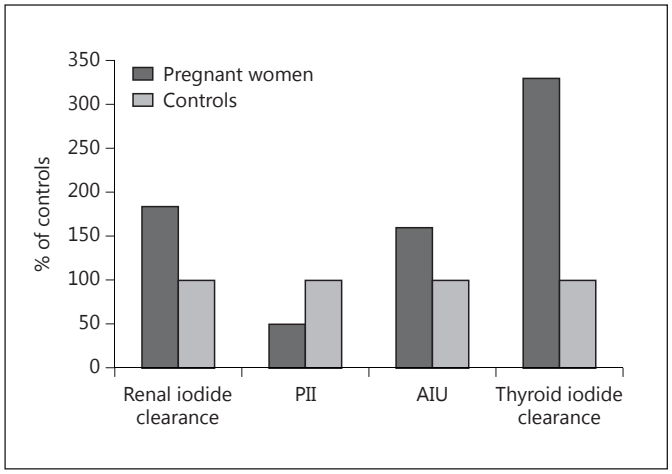

Fig. 1. Relative changes in maternal renal iodide clearance, PII and AIU in the thyroid gland, and thyroid iodide clearance in 13 pregnant women versus 13 nonpregnant controls. Data are from Aboul-Khair et al. [6].

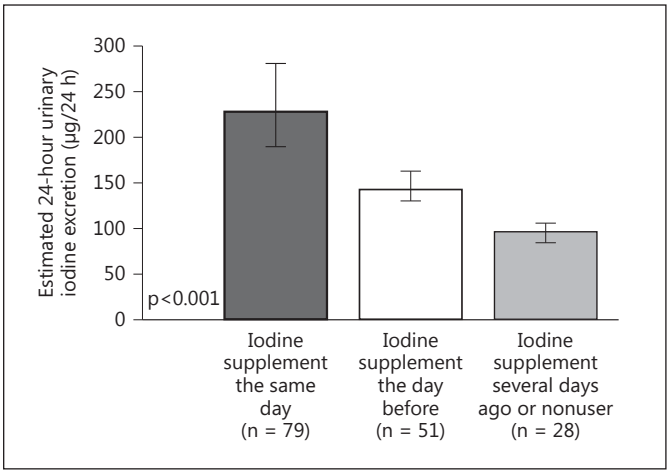

Fig. 2. Median (95% CI) estimated 24-hour urinary iodine excretion in Danish pregnant women stratified by the time of most recent iodine supplement intake prior to spot urine sampling. The p value is the result of the Kruskal-Wallis test (same day vs. the day before vs. several days ago/nonuser). Data are from Andersen et al. [16].

have occurred on this specific day. In our study of pregnant women [16], we collected spot urine samples from a group of pregnant women both on the day they visited the hospital for obstetric ultrasound and another day at home. The median UIC was 84 µg/l in the hospital and 133 µg/l at home.

UIC in a spot urine sample varies with fluid intake (urine volume) and, since creatinine is excreted in the urine at a relatively constant rate, it can be used to adjust for differences in fluid intake, as previously discussed [17]. We also measured urinary creatinine concentration in the Danish pregnant women investigated [16], and when the urinary creatinine concentration was used to estimate 24-hour urinary iodine excretion in these women, no difference was observed between sampling in the hospital and at home. Thus, the difference in UIC was mostly caused by differences in fluid intake [16]. Some obstetric clinics directly recommend excessive fluid intake to pregnant women before an obstetric ultrasound to allow better visualization of the fetus. Obviously, this will lead to a low iodine concentration in a subsequent spot urine sample. One way to overcome such a potential source of bias would be to include the pregnant women in the study the day they visit the hospital and to provide vials for urine sampling, but urine sampling should be performed later on a typical day at home.

A special methodological problem is the evaluation of iodine status in pregnant women who take a daily iodine-containing supplement. A considerable fraction of an oral load of iodine is excreted in urine within the next 12 h [18]. Thus, a spot UIC would depend much on whether the urine is collected before or some hours after the daily iodine supplement intake. Figure 2 illustrates how the timing of urine sampling in relation to supplement intake affected estimated 24-hour urinary iodine excretion in our Danish study [16].

It has been discussed if urinary iodine excretion in nonpregnant adults and in schoolchildren is useful for the evaluation of iodine status in pregnant women living in the same area [19]. In our Danish study, we found no difference between the median UIC in pregnant women, their male partners and children when urine sampling was performed at home under similar conditions (fig. 3) [16]; however, iodine supplement use was much more frequent among pregnant women than among male partners and children [16]. Other investigators have reported different results, with a higher median UIC in children than in pregnant women [20, 21]. In these studies from Thailand and India [20, 21], the children and pregnant women shared one or more meals, but the time and location of spot urine sampling may have differed. Moreover, the pattern of supplement intake was different compared to our Danish study.

The question of a possible shift in UIC in pregnancy is linked to a possible change in dietary habits during pregnancy, and the likelihood of such shift may differ from

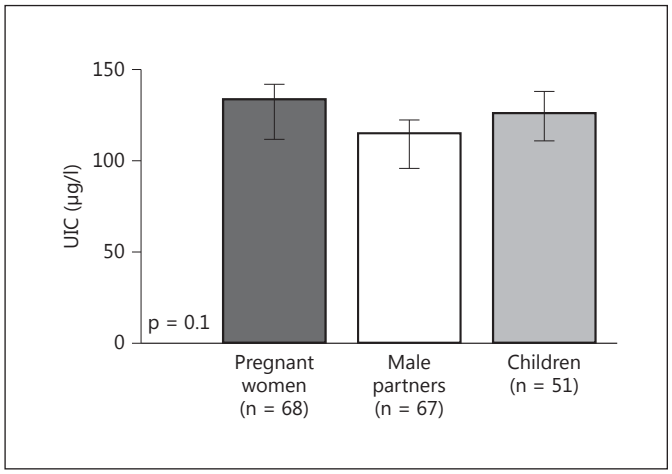

Fig. 3. Median (95% CI) UIC in Danish pregnant women, their male partners and children when all individuals performed urine sampling at home under similar conditions. The p value is the result of the Kruskal-Wallis test (UIC pregnant women vs. male partners vs. children). Iodine supplement users: pregnant women (n = 59), male partners (n = 10), children (n = 13). Kruskal-Wallis test (UIC pregnant women vs. male partners vs. children) in iodine supplement users, p = 0.5, and in iodine supplement nonusers, p = 0.4. Data are from Andersen [3] and Andersen et al. [16].

country to country. If women change their diet with intake of more or less iodine-rich food during pregnancy, their 24-hour urinary iodine excretion will change, and if they change their fluid intake, their UIC will change. Thus, no universal rule can be given on the association between UIC in schoolchildren and in pregnant women. Similarly, the reports on the change in UIC during the three trimesters of pregnancy are diverse [3], with some authors reporting an increase [22–26], other researchers a decrease [27–30] and still other authors observing no change [31–35] between the different trimesters of pregnancy. No consistent pattern in the median UIC by trimester of pregnancy can be derived from these studies. Changes in UIC during pregnancy may reflect changes in dietary iodine intake and/or fluid intake, which are the main determinants of UIC.

When Should Pregnant Women Take Iodine-Containing Supplements?

A main consensus in the WHO/UNICEF/ICCIDD guidance on achieving adequate iodine intake in populations is that salt iodization is the key strategy [5]. Supplements should only be the solution when salt iodization fails. This is in line with the general recommendations given by Geoffrey Rose [36] when delineating the strategy of preventive medicine: mass exposures to risk require mass remedies. A targeted approach may assist, but it cannot be sufficient. Whereas the salt iodization is a so-called population-based strategy, the advocation of supplements would be a more individualized approach. As reviewed by Rose [36], population-based strategies are preferable so long as they address a population-wide problem. In such situations, an individualized approach would tend to be expensive and less effective, especially leaving the most vulnerable groups less covered.

In our Danish study of pregnant women with a low dietary iodine content, intake of iodine-containing supplements was less common among women with a low level of education [37]. Very limited data are available on the predictors of iodine supplement use in pregnancy as the majority of studies investigated the predictors of UIC and, thus, a contribution of both dietary and supplementary iodine intake. However, in a study from Australia [38], general use of dietary supplements and knowledge on the importance of iodine were the main predictors of iodine supplement intake in pregnant women. Further studies are needed to examine predictors of iodine supplement intake in pregnancy as such analyses may indicate population groups at risk of ID.

An important question is how to proceed if the population in general has an adequate iodine intake, with the median UIC ≥100 µg/l, but the median is below the 150 µg/l recommended in pregnancy. Should all pregnant women take an iodine-containing supplement in such populations? Or should salt iodization be increased to a level leading to a median UIC ≥150 µg/l in women who may become pregnant? The consensus reached by the WHO/UNICEF/ICCIDD was that pregnant women should not be recommended to take iodine-containing supplements if the population in general is iodine sufficient, with a median UIC ≥100 µg/l for at least 2 years [39]. In this scenario, it is expected that the iodine stores of the thyroid gland are sufficient to cover the extra needs during pregnancy. Details on the recommendation given by the WHO/UNICEF/ICCIDD are shown in table 2 [39].

However, guidance differs between scientific societies, e.g. the American Thyroid Association has specifically recommended that pregnant women living in the USA should take iodine-containing supplements [40], even if the US population is in general iodine sufficient [24, 41, 42]. In a recent study of 141 US women living in Wash-

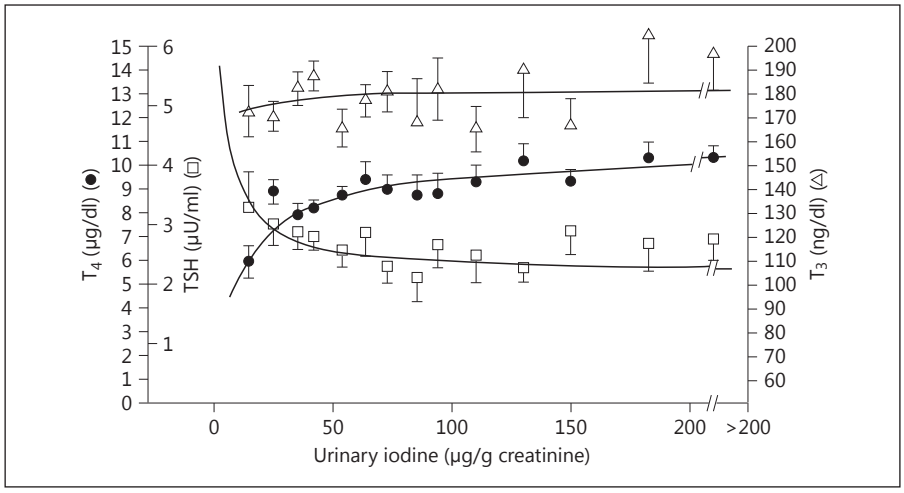

Fig. 4. Serum T_3, T_4 and TSH concentrations as a function of urinary iodine excretion in 250 pregnant women in an iodine-deficient area (Chile). Reproduced with permission from Silva and Silva [53].

Table 2. Strategies to control ID in pregnant women

Status of salt iodization in the country or in a region within the country	Approach to provide additional iodine to pregnant women
Category 1 More than 90% of households use iodized salt Median UIC in school-aged children >100 μg/l	Continue universal salt iodization
Category 2 20–90% of households use iodized salt Median UIC in school-aged children 21–99 μg/l	Individual iodine supplementation
Category 3 <20% of households use iodized salt Median UIC in school-aged children <20 μg/l	Individual iodine supplementation

Data are from [39].

ington DC and participating in preconception screening and counseling, the median UIC was 101 μg/l [43]. The European Thyroid Association stated in its 2014 guidelines on the management of subclinical hypothyroidism in pregnancy [44] that 'a sufficient iodine intake is usually provided by supplementing euthyroid pregnant and lactating women with formulas containing 150 μg iodine/day, ideally before conception'. Both the 2007 [45] and the 2012 [46] Endocrine Society guidelines on thyroid dysfunction in pregnancy stressed the importance of considering the iodine status in the country in general when deciding on iodine supplementation, and they cite the WHO-recommended stratification of countries according to general iodine status [39]. The discordance in guidance from different authorities most likely reflects the lack of data to properly indicate when and which dosage of iodine to recommend in pregnancy.

What Level of Iodine Intake in Pregnancy Is Associated with a Risk of Fetal Brain Damage?

Descriptions of areas where cretinism was previously common (endemic cretinism) noted that urinary iodine excretion in such areas was well below 20 μg/day [47, 48]. However, more recent studies have suggested that neurocognitive [49, 50] and behavioral [51] abnormalities may be caused by a much lower degree of ID. It is complicated and expensive to perform sufficiently powered studies of the association between maternal iodine intake in pregnancy and long-term subtle neurocognitive and behavioral abnormalities in children, and simpler models may be useful for the initial evaluation of risk.

The accepted hypothesis behind ID-related brain damage is insufficient thyroid hormone production in

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the pregnant woman in combination with late pregnancy fetal hypothyroidism and infant hypothyroidism caused by ID [52]. Thus, a simpler way to evaluate the risk is to study the associations between maternal iodine intake and thyroid function in the mother and the child.

A number of such studies suggest that the critical level of urinary iodine excretion at which thyroid dysfunction may start to develop in pregnancy is around 50 μg/l. Figure 4 shows the results of a study performed in Chile [53] at a time when iodine intake was rather low in many inhabitants. In this study [53], thyroid function and urinary iodine excretion were measured in groups of pregnant women with different levels of iodine intake. As depicted, an increase in the prevalence of maternal hypothyroidism occurred when urinary iodine excretion was below 50 μg/day. A recent large study from China [54] investigated 7,190 pregnant women in early pregnancy (weeks 4–8) and observed that the subgroup of women with a spot UIC <100 μg/l had a significantly higher prevalence of overt hypothyroidism, but not of subclinical hypothyroidism or isolated hypothyroxinemia, compared to women with a UIC in the range of 150–249 μg/l.

These results are corroborated by randomized interventional studies performed in Denmark [31] and Belgium [55]. The studies included women living in areas with mild-to-moderate ID and in both studies iodine supplementation in pregnancy gave a moderate but statistically significant improvement of thyroid function in the mother. In the Danish study [31], a random sample of 54 pregnant women who lived in the low-iodine intake city of Randers, and who were not habitual users of supplements, were randomized to take either a 200-μg or no iodine supplement daily. The women who took supplements had an 18% lower serum TSH (statistically significant) in late pregnancy (all participants had TSH values within the laboratory reference range), and a 3% higher fT_4 (not statistically significant). The median UIC in the last trimester of pregnancy was around 40 μg/l in the women who did not receive supplements.

In the Belgian study [55], 180 women were selected because they had biochemical signs of high thyroid activity (low fT_4, high serum Tg, elevated serum T_3/T_4 ratio) in early pregnancy and were randomized to receive either a 100-μg iodine supplement daily or none at all. The women who did not receive a supplement had a median UIC of 30 μg/l in late pregnancy, and iodine supplementation led to a significantly reduced increase in serum TSH (an increase of around 0.4 vs. 1.1 mU/l in nonsupplemented women) as well as thyroid volume in the pregnant women. Somewhat unexpectedly, the iodine supplements did not alter serum TSH or fT_4 in cord blood in either of the studies [31, 55].

Is Iodine Intake Critically Low in Pregnancy if the Population Suffers from Mild ID?

Mild ID is characterized by a median UIC in the range of 50–99 μg/l in nonpregnant adults and school-aged children (table 1) [5]. No interventional study has convincingly demonstrated a better outcome of pregnancy if pregnant women living in such areas of mild ID take iodine supplements [56]. In the Controlled Antenatal Thyroid Screening (CATS) study [57], 21,846 pregnant British and Italian women were screened for thyroid dysfunction in early pregnancy, and about 5% of the women who had deviations in serum TSH (above the 97.5th percentile) and/or serum fT_4 (below the 2.5th percentile) participated in a randomized prospective study of L-T_4 supplementation, which was initiated at a median of 13 weeks of gestation. At the time of the study, the British and Italian women studied were by definition iodine deficient. Among 487 women included, the median UIC was 72 μg/l (95 μg/l in the British and 54 μg/l in the Italian women) [58]. This study was not conducted to investigate iodine supplementation. However, about 100 μg of the daily starting dose of 150 μg of L-T_4 given in the study consisted of iodine, which is released during T_4 metabolism and enters the body iodine pool. Moreover, any impairment of maternal thyroid function caused by ID in the British and Italian mothers participating in this study would have been resolved in the treatment group by the L-T_4 supplement. At the age of 3 years, L-T_4 supplementation had not improved cognitive function in the children in either of the countries [57]. Thus, the CATS study suggests against an improved outcome of pregnancy with iodine supplementation in British and Italian mothers with a median UIC of 95 and 54 μg/l, respectively. More prolonged follow-up of the children [59] in this study may lead to a modification of this conclusion.

Possible Adverse Effects of Iodine Supplementation in Pregnancy?

In general, iodine supplementation is not recommended in individuals suffering from autoimmune thyroid disease. In rats exposed to acute high levels of iodine a transient reduction in the synthesis of thyroid hor-

mones was observed and referred to as the Wolff-Chaikoff effect [60]. However, this is a transient phenomenon as a downregulation of NIS transport of iodide into the thyroid gland will lead to escape from the Wolff-Chaikoff effect [61]. However, individuals with autoimmunity or previous thyroid disease may fail to escape from the Wolff-Chaikoff effect following exposure to high levels of iodine, and hypothyroidism may develop [62, 63]. Also, hyperthyroidism may develop in susceptible individuals (e.g. relapse of Graves' disease) following high intake of iodine [62]. On the other hand, the risk of adverse effects to a sudden moderate change in iodine intake seems negligible in healthy individuals not suffering from thyroid disease.

The previously mentioned study from China [54] looked into the optimal and safe upper limit for iodine intake in 7,190 pregnant women (median UIC 152.6 μg/l). In this study population [54], the prevalence of maternal subclinical hypothyroidism was significantly higher among women with a UIC >249 μg/l, isolated hypothyroxinemia was more frequent among women with a UIC ≥500 μg/l, and the prevalence of thyroid peroxidase antibodies and Tg antibodies showed a U-shaped curved with the lowest prevalence in the group of women with UIC in the range of 150–249 μg/l. Increasing the iodine intake in a population (e.g. from universal salt iodization) has been associated with a general increase in TSH [64] and a higher prevalence of thyroid peroxidase and Tg antibodies, particularly among young women [65]. The potential significance of such changes is not known. However, based on current knowledge iodine intake in a population should not be higher than necessary to prevent ID disorders [62]. Notably, there is no indication that iodine supplementation would do harm to pregnant women with a normal thyroid function, even if their iodine intake was already sufficient, but it would not be necessary.

Spread of Iodine Intake within a Population

The results of the interventional studies mentioned may be taken to indicate that iodine supplement intake is not necessary in pregnant women living in areas with mild ID (median UIC 50–99 μg/l). However, as recently reviewed by Taylor et al. [56], there are indices suggesting positive effects, even if large interventional studies are needed. Moreover, a strategy of not recommending iodine supplementation in populations of pregnant women with a median UIC in the range of 50–99 μg/l may leave a subgroup of pregnant women with a high risk of inadequate iodine intake. Studies of iodine-deficient populations were previously mostly done in low income areas where diet was rather uniform and consisting of local agricultural products. Thus, the distribution of iodine intake among individual inhabitants would have been quite narrow.

Such a dietary pattern is rapidly changing in many areas of the world, and dietary preferences may be highly variable. This will lead to a much greater range of iodine intake in a population. Even in generally iodine-sufficient populations, people with ID caused by peculiar dietary habits have been identified [66, 67]. The discrepancies in iodine intake may leave some pregnant women with a dangerously low iodine intake, even if the population in general is only mildly iodine deficient. For example, women who do not consume dairy products may have a very low iodine intake if cow's milk is a main source of iodine in the general population [66–68]. Moreover, smoking may hamper the utilization of iodine [69, 70]. Thus, women living in mildly iodine-deficient areas according to the WHO/UNICEF/ICCIDD definition [5] (table 1) should, in our opinion and in line with the consensus reached by the WHO/UNICEF/ICCIDD [39] (table 2), take iodine-containing supplements during pregnancy.

Conclusion

Based on available evidence, we find that the consensus reached by WHO/UNICEF/ICCIDD [39] in 2007 is a valid guidance on the individual use of iodine supplementation in pregnancy. As a general rule, women living in a population with a median UIC at or above 100 μg/l are not in need of iodine supplementation in pregnancy. If the population median UIC is below 100 μg/l, pregnant women should take iodine-containing supplements until the population in general has been iodine sufficient for at least 2 years by way of universal salt iodization.

Disclosure Statement

The authors report no conflicts of interest.

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