



# Iodine nutrition in pregnant and breastfeeding women: sufficiency, deficiency, and supplementation

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## Abstract

Iodine is a micronutrient used by the thyroid gland to produce thyroid hormones, which manage different aspects of body metabolism. Humans depend on exogenous sources of iodine to maintain the normal concentration of thyroid hormones. Pregnancy alters iodine turnover and is associated with significant changes in thyroid function. Daily iodine requirement during pregnancy increases to 250 µg, compared with 150 µg for nonpregnant women. According to recent guidelines of scientific organizations, to improve maternal thyroid status and to prevent child neurocognitive defects, all pregnant and breastfeeding women should take 150 µg of iodine supplementation, not only in iodine-deficient regions but also in iodine-sufficient areas. However, some recent studies have confirmed that iodine supplementation of mildly iodine-deficient pregnant women has no clear benefits as concerns maternal thyroid function or child neurodevelopment.

**Keywords** Iodine supplementation · Pregnancy · Lactation · Iodine deficiency · Iodine status

## Introduction

Iodine is used by the thyroid gland to produce thyroid hormones. For women, iodine is necessary for optimal function of the reproductive system and for normal fetal growth and development [1]. There is consistent evidence that severe iodine deficiency during pregnancy and lactation is associated with impaired neurocognitive development of the fetus and neonate [2]. However, it is still uncertain whether mild-to-moderate maternal iodine deficiency may have a long-term negative impact on child neurodevelopment. Observational studies indicate that correction of mild-to-moderate iodine deficiency in pregnancy has substantial health and economic benefits.

## Material and methods

This is a narrative review. We searched PubMed, Embase, Ovid, Medline, and Cochrane Central in May 2019, for all studies of iodine nutrition during pregnancy and lactation with the terms Pregnancy, Lactation, Iodine deficiency, Iodine supplementation, Iodine status, and Iodized salt. The search was limited to publications in the English language. The search returned a total of 238 publications. An additional 47 potentially relevant articles were identified by checking the references of included studies and relevant review articles. After removing duplication, 205 articles remained. Forty-five articles were excluded because they did not meet the inclusion criteria. Finally, a total of 160 articles were included in this review.

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## Iodine turnover

Humans depend on exogenous sources of iodine [3, 4]. In conditions of iodine sufficiency, the thyroid gland takes up less than 10% of absorbed iodine, whereas in chronic iodine deficiency, this fraction exceeds 80% [5, 6]. In lactating women, iodine is concentrated in the mammary gland and is secreted into breast milk to provide iodine for the newborn [7, 8]. Approximately 90% of absorbed iodine is finally excreted by

the kidney, which is why urinary iodine concentration (expressed in  $\mu\text{g/L}$ ) correlates well with the level of recent iodine intake [9]. Based on the recommendation of the World Health Organization (WHO) and the Iodine Global Network (IGN), the median urinary iodine concentration (UIC) in schoolchildren is the main indicator of iodine nutrition of a community. A UIC of between 100 and 199  $\mu\text{g/L}$  in school-aged children and adults and between 150 and 249  $\mu\text{g/L}$  in pregnant women is considered adequate [10].

## Thyroid function during pregnancy

Pregnancy alters thyroid physiology [11, 12], and increased circulating estrogen during pregnancy increases thyroid binding globulin (TBG) 2- to 3-fold in response to this phenomenon. Also, because of thyroid stimulating hormone (TSH) receptor stimulation by human chorionic gonadotropin (hCG), thyroid hormone production increases by 50% during early gestation in pregnant women (Fig. 1). Another change during pregnancy is degradation of T4 to bio-inactive reverse triiodothyronine (rT3) by the placental type 3 inner ring deiodinase [13]. On the other hand, the glomerular filtration rate of iodide increases by 30 to 50% in early pregnancy. In the fetus, the placenta is a highly specialized organ whose primary function is to promote the exchange of nutrients and oxygen between maternal and fetal blood [14]. In 2006, Cosmo and co-workers for the first time described the presence of sodium-iodide symporter ( $\text{Na}^+/\text{I}^-$  symporter (NIS)) in placental cells [15]. NIS expression in placenta is at lower levels than that in the thyroid, and it mediates the active uptake of iodide by the developing fetus for its proper thyroid hormone synthesis [16]. Altogether, these physiological changes, along with the need of the fetal thyroid gland for iodine to produce thyroid hormones during the second half of gestation, increase iodine requirements in normal pregnancy [17, 18]. Failure to meet

this increased iodine demand results in an insufficient supply of thyroid hormones to the developing brain, leading to permanent brain damage and mental retardation in the newborn [19, 20].

## The burden of iodine deficiency

Inadequate iodine intake has negative effects on the physical and mental development of millions of people living in iodine-deficient areas around the world [21]. The term iodine deficiency disorders (IDD), introduced by Basil Hetzel in 1983, has transformed the world's understanding of the problem, which leads to disorders ranging from endemic goiter to numerous other conditions [22] (Table 1). The brain is particularly sensitive to iodine deficiency during its formation in early fetal and postnatal life [23, 24]. Overt hypothyroidism in pregnant women due to severe iodine deficiency is also associated with other adverse events, including preeclampsia, gestational diabetes, gestational hypertension, and spontaneous abortion [25]. There is increasing concern that mild-to-moderate iodine deficiency during pregnancy may lead to cognitive deficits and learning disabilities in children. The association between subclinical hypothyroidism due to mild-to-moderate iodine deficiency and obstetric complications is less clear. Mannisto et al., in a retrospective study in 223,512 singleton pregnancies in the USA, found an increased risk for gestational diabetes with subclinical hypothyroidism [26]. A study of 1170 pregnant women [27] and two meta-analyses have supported this association [28, 29]. Fetal death was more frequent in pregnant women with TSH greater than 6.0 mU/L according to studies by Allan et al. [30] and Benhadi et al. [31]. A study by Negro et al. also indicates a significant increase in miscarriage rate in negative antithyroid peroxidase antibody (TPO-Ab) women whose first trimester TSH was 2.5–5.0 mU/L vs less than 2.5 mU/L [32]. In contrast, in a retrospective study in which 240 women with subclinical hypothyroidism were compared with 10,518 controls, no difference in miscarriage rates was observed between the two groups [33].

At the beginning of the second trimester, the fetal thyroid gland begins to synthesize thyroid hormones, and, at around 18–20 weeks of gestation, the pituitary-portal vascular system in the fetus completes its development [34]. Fetal and newborn neurogenesis and neurodevelopment are depicted in Fig. 2. In general, pregnant women need to increase their iodine intake by 50% to produce adequate thyroid hormone to meet fetal requirements. In areas of iodine sufficiency, the maternal thyroid gland increases its iodide uptake to maintain adequate intrathyroidal stores. In moderate-to-severe iodine deficiency, however, such adaptive mechanisms may fail to maintain adequate iodine stores and this may ultimately lead to thyroid dysfunction and goiter [35]. In summary, it is clear

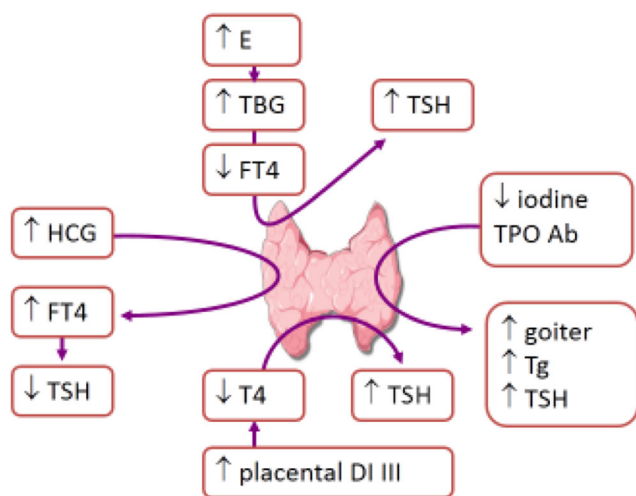


Fig. 1 Factors of thyroid stimulation during pregnancy

**Table 1** Consequences of iodine deficiency in pregnant mother, fetus, and neonate [22]

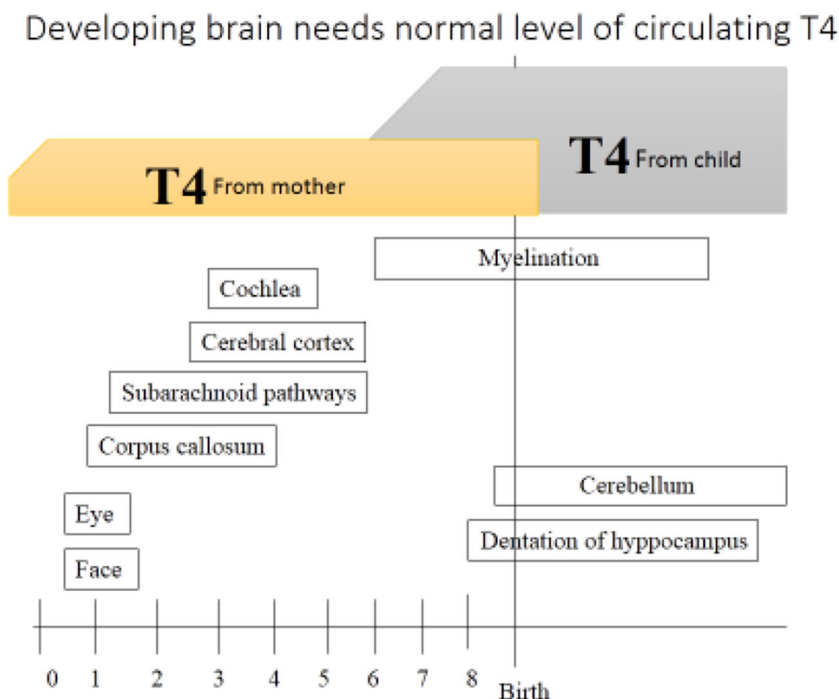
Life stage	Major disorders
Pregnant mother	Goiter, abortion, stillbirth, increased infant mortality, problems in normal reproduction in adult life
Fetus	Goiter, congenital anomalies, increased infant mortality
Neonate	Goiter, hypothyroidism, psychomotor defects, various degrees of cretinism, retarded physical development, impaired mental development, impaired intellectual performance, increased susceptibility of the thyroid gland to nuclear radiation

that low concentrations of maternal T<sub>4</sub>, in particular, can hinder the development of the fetal brain. Hypothyroxinemia of a euthyroid mother with moderate-to-severe iodine deficiency can damage the developing brain in the first half of pregnancy and can continue in the second half of pregnancy when the condition is further aggravated by hypothyroidism in the fetus, manifested by lower IQ in the offspring.

There is consistent evidence that severe maternal iodine deficiency is associated with abnormal neuropsychological development in children [19]. However, it is still uncertain whether mild-to-moderate maternal iodine deficiency affects cognitive function in the offspring [36] and the results of cohort studies have been somewhat variable yielding controversial results [37–41]. There are some studies reporting that maternal iodine deficiency in mild-to-moderate iodine deficient areas can result in less severe, but measurable, long-lasting impacts, especially during the neonatal period, affecting the intellectual development of the child [42–45]. In our study, children from iodine-deficient areas of Iran showed neurological and auditory retardation and psychomotor

impairments [44]. In a study by Abel MH.et al., suboptimal maternal iodine intake was associated with impaired child neurodevelopment at 3 years of age in the Norwegian Mother and Child Cohort Study [46]. Recently, a meta-analysis was performed by Levie et al. using data from three European pregnancy cohorts: Generation R in the Netherlands, the Infancia y Medio Ambiente Project (INMA) in Spain, and the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK. Median urinary iodine concentrations were 159 µg/L in the Generation R cohort (iodine-sufficient), 128 µg/L in the INMA cohort (mildly iodine-deficient), and 96 µg/L in ALSPAC (moderately iodine-deficient). Low urinary iodine was associated with poorer child verbal IQ scores. There were no associations of maternal iodine status with child nonverbal IQ [47]. Brain and central nervous system development takes place from the second trimester of pregnancy to 3 years of age. Breastfed infants depend solely on an adequate supply of iodine in breast milk for the synthesis of thyroid hormones, breast milk iodine concentration depending on maternal dietary intake [48]. Thus,

**Fig. 2** Major events in fetal and neonatal central nervous system development



low maternal iodine intake inevitably renders lactating women and their breastfed infants prone to iodine deficiency. It is therefore clear that during this period, maternal iodine intake should be optimal in order to supply adequate iodine to the developing fetus.

## Iodine requirements during pregnancy and lactation

Many studies have established the benefits of iodine supplementation during pregnancy in areas of severe iodine deficiency [49–51]. In a meta-analysis of five studies by Taylor et al., it was shown that when iodine supplementation was introduced as early as at 4 weeks' gestation, it was associated with markedly increased IQ in children [43]. Iodine requirements of women during pregnancy and lactation are increased to provide adequate iodine for the fetus and neonate (Table 2). Salt iodization is one of the preferred strategies to eradicate iodine-deficiency disorders worldwide. It is generally assumed that the iodine requirements of all population groups are covered in settings where universal salt iodization (USI) has been implemented for more than 2 years and the median UIC in school-age children (6–12 years) is  $\geq 100 \mu\text{g/L}$  [10]. However, studies assessing UIC in school-age children in parallel with that in pregnant women deliver mixed results. Some studies report adequate iodine intake in all population groups [52, 53], whereas others report iodine sufficiency in school-age children, but iodine deficiency in pregnant and lactating women [54–56]. A recent national survey on iodine status in Iran by Hossein Delshad et al. revealed that while school-age children were iodine-sufficient, pregnant women were moderately iodine-deficient [57]. A Norwegian study has also produced similar results [58]. In China, the median iodine excretion in pregnancy was  $50 \mu\text{g/L}$  lower than in nonpregnant women, despite adequate iodine intake in the general population [59]. It has also been reported that even in the USA, where pregnant women have an adequate median UIC ( $173 \mu\text{g/L}$ ), the lower 95% confidential interval found UIC

to be below  $150 \mu\text{g/L}$  [60]. Furthermore, a report from the Boston area showed that approximately half of pregnant women had UICs below  $150 \mu\text{g/L}$  and 9% had values below  $50 \mu\text{g/L}$  [61]. In a meta-analysis by Nazeri et al., it was demonstrated that the median UIC of lactating mothers of most countries with voluntary programs of USI, and also in countries with mandatory iodine fortification are still within the iodine deficiency range [62]. In addition, studies from the northeast of England [63] and from Australia [64], in which the populations are assumed to be iodine-replete, demonstrated insufficient UIC in about 50% of pregnant women. In contrast, a recent cross-sectional multicenter study revealed that USI provides sufficient dietary iodine to achieve adequate iodine nutrition during the first 1000 days [53]. In this international, multicenter study in three countries (China, the Philippines, and Croatia) with mandatory USI legislation, six population groups (5860 participants) were assessed for UIC and thyroid function. The salt iodine concentration of households was adequate ( $15\text{--}40 \text{ mg/kg}$ ) in these areas. The median UIC showed adequate iodine nutrition in all population groups, except for excessive iodine intake in school-age children in the Philippines and borderline low intake in pregnant women in Croatia. Taken together, these findings suggest that USI programs may not be adequate for individual pregnant women, especially in countries in which UIC programs have been recently introduced or in conditions with unstable dietary iodine intake.

To meet the daily iodine requirements, the WHO, UNICEF, IYF [65], and the American Institute of Medicine [66] have provided daily iodine intake recommendations for the different age groups (Table 3). Excessive iodine intake can also be harmful because it inhibits thyroid hormone synthesis and its release into the circulation (the Wolff-Chaikoff effect) [67]. It is difficult to determine the threshold upper limit of iodine intake because the amount of iodine intake before exposure to iodine excess has detrimental effects. The WHO considers iodine intake  $> 500 \mu\text{g/day}$  to be excessive [68], while the US Institute of Medicine and the European Food Safety Agency recommend this level at  $600 \mu\text{g/day}$  and  $1100 \mu\text{g/day}$ , respectively [66, 69].

**Table 2** Iodine requirement in pregnancy and lactation ( $\mu\text{g/day}$ )

During pregnancy	
Basal	150
40–50% increased T4 requirements	50–100
Transfer of T4 and iodine from mother to fetus	50
Increased renal clearance of iodine	?
Total	250–300
During lactation	
Basal	150
$0.5\text{--}1.1 \text{ L milk/day} \times 150\text{--}180 \mu\text{g iodine/L}$	75–200
Total	225–350

## Iodine supplementation during pregnancy and lactation

Most people receive relatively small amounts of iodine in their diet, hence the need for an additional source to provide adequate iodine for their daily requirements. Fortified salt, bread, and water are the main sources of iodine. WHO recommends fortification of all food-grade salts with iodine as an effective and safe strategy for control and prevention of IDD for those living in both iodine-deficient and iodine-sufficient areas [70]. In a recent cross-sectional multicenter study by Susanne Dold

**Table 3** Recommended daily iodine intakes for different age groups [65, 66]

Age and population group	WHO/UNICEF/IGN	US Institute of Medicine
0–5 years	90	–
6–12 years	120	–
> 12 years	150	–
0–12 months	–	110–130
1–8 years	–	90
9–13 years	–	120
> 14 years	–	150
Pregnant women	250	220
Lactating women	250	290

WHO, World Health Organization; UNICEF, United Nations Children's Fund, IGN, Iodine Global Network, US, United States

et al., it was shown that USI provides sufficient dietary iodine to achieve adequate iodine nutrition during the first 1000 days [53].

In regions of severe iodine deficiency, iodine supplementation of pregnant women has beneficial effects on the neurodevelopment of the fetus and neonate and is associated with normal central nervous system development [71], although the benefit of iodine supplementation in areas with mild-to-moderate deficiency is still uncertain. The earliest study conducted was a randomized controlled trial (RCT) in Papua New Guinea in the early 1970s [72]. In this study, pregnant women living in a severely iodine-deficient region were administered injections of lipiodol, a solution of iodinated oil; compared with untreated women, the rates of fetal death and endemic cretinism were low for up to 5 years in the study group [73]. Six controlled trial studies in several moderately iodine-deficient European regions have also assessed the effects of iodine supplementation during pregnancy [74–79]: they report that maternal TSH and the infant's thyroid gland volume decreased and neonatal psychological and neurocognitive measures improved in supplemented mothers, compared with those born to nonsupplemented ones. In contrast, a study from Valencia, Spain, by Murcia et al., indicates that higher maternal iodine intake was associated with lower scores on the Psychomotor Development Index in their children at the age of 1 year [40]. Another study by this group also indicates that iodine supplementation of mildly iodine-deficient mothers does not improve infant neuropsychological development at 1 year of age [42]. Recently, this group also conducted a prospective cohort study and found an association between low maternal urinary iodine and lower cognitive scores in childhood (only when corrected for creatinine), though iodine supplementation does / did not appear to improve children's neurodevelopment at 4–5 years [80]. Two published systematic reviews of randomized controlled trials

by Zhou et al. [81] and Harding et al. [71] indicate a lack of quality evidence of the effect of prenatal or preconceptional iodine supplementation on children's growth and cognitive function. There were insufficient data to reach any meaningful conclusions on the benefits and harms of routine iodine supplementation in women before, during, or after pregnancy in regions with mild-to-moderate iodine deficiency since none of the RCTs conducted in those regions assessed developmental outcomes of children. However, there is some evidence from nonrandomized intervention studies suggesting that iodine supplementation in pregnancy in regions of mild-to-moderate iodine deficiency may improve cognitive function in children [74, 76, 78]. Conversely, adverse effects on child development in relation to iodine supplementation in pregnancy have also been reported from cohort studies [56]. Taken together, the effect of iodine supplementation in mildly iodine-deficient pregnant women on neurodevelopment in children is still a matter of debate. It is thought that supplementation of potassium iodine, starting in the first trimester of pregnancy, may have a positive effect on infant psychomotor development. But current WHO recommendations suggest that although iodine supplementation during pregnancy is safe, it might not be justified in mildly iodine-deficient pregnant women residing in countries with iodine sufficiency [82]. This concept has been confirmed in a recently published randomized, placebo-controlled trial by Gowachirapant et al. In this study, pregnant women in Bangalore, India, and Bangkok, Thailand, were randomly assigned to receive 200 µg iodine orally once a day or placebo until delivery. In this trial, daily iodine supplementation in mildly iodine-deficient pregnant women living in iodine sufficient areas had no effect on child neurodevelopment at age 5–6 years [83]. It is suggested that pregnant women with sufficient iodine intake before and during pregnancy generally have adequate intrathyroidal iodine storage and can adapt to the increased demand for thyroid hormone throughout gestation for normal in utero development of the fetus, but in the setting of even mild iodine deficiency, total body iodine stores decline gradually from the first to the third trimester of pregnancy [84].

In some countries, the effects of iodine supplementation at different doses have been examined among lactating mothers [75, 85–87]. In the USA, 150 µg iodine supplementation of lactating mothers indicated that they had not received the recommended intake of iodine [85]; in New Zealand also, daily supplementation of either 75 or 150 µg iodine for iodine-deficient lactating mothers was insufficient to provide optimal iodine intake [75]. Even in Morocco, with moderate-to-severe iodine deficiency, median UIC in lactating women supplemented with 400 mg iodized oil remained < 100 µg/L, although it was significantly higher compared with the placebo group [87].

## Conclusion

Adults need 150 µg iodine per day, ranging from 90 to 290 µg per day, based on the individual's age and physiological status. Dietary modifications are necessary when a woman becomes pregnant, such as increasing the intake of iodine, which helps to ensure optimum fertility, conception, and pregnancy. Adequate intake of iodine in this period is associated with proper functioning of the thyroid gland. Intrathyroidal iodine stores in women should be adequate thanks to USI programs, although they may not always adequately fulfill the increase in iodine demand during pregnancy and breastfeeding. The main method of iodine prophylaxis, in pregnancy also, is USI. However, particularly if there is not sufficient coverage of households with iodized salt, additional measures, such as oral supplementation with potassium iodide tablets, are necessary in pregnant women to provide adequate iodine nutrition. Prevention of fetal iodine deficiency is feasible, provided that an iodine supply of 200–300 µg/day to the mother is ensured before and throughout gestation as well as during the lactating period.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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