Hormones (2020) 19:179–186
https://doi.org/10.1007/s42000-019-00160-2

REVIEW ARTICLE

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

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Received: 3 August 2019 / Accepted: 12 November 2019 / Published online: 27 November 2019

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.

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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.

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 μg/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 μg/L in school-aged children and adults and between 150 and 249 μg/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 (Na^+/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

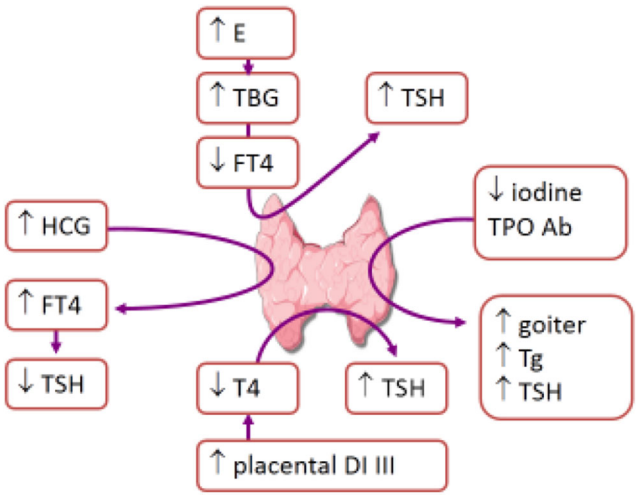

Fig. 1 Factors of thyroid stimulation during pregnancy

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

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_4, 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 neuropsychlogical 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,

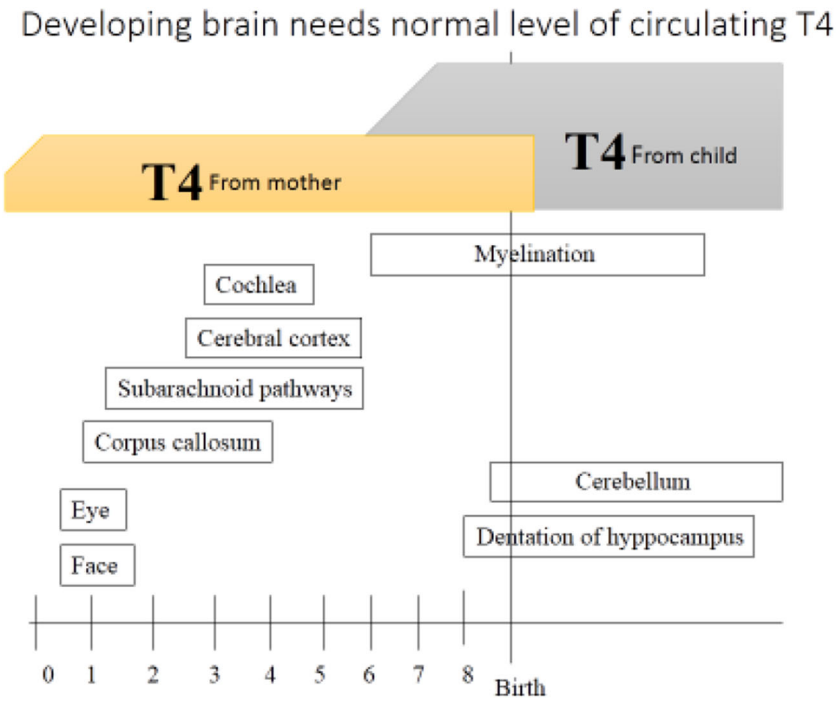

Fig. 2 Major events in fetal and neonatal central nervous system development

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 ≥ 100 μg/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 μg/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 μg/L), the lower 95% confidential interval found UIC to be below 150 μg/L [60]. Furthermore, a report from the Boston area showed that approximately half of pregnant women had UICs below 150 μg/L and 9% had values below 50 μg/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 (15–40 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, ING [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 μg/day to be excessive [68], while the US Institute of Medicine and the European Food Safety Agency recommend this level at 600 μg/day and 1100 μg/day, respectively [66, 69].

Table 2 Iodine requirement in pregnancy and lactation (μg/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
0.5–1.1 L milk/day × 150–180 μg 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 Muricia 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.

Acknowledgments The authors wish to acknowledge Ms. Niloofar Shiva for her critical editing of the English grammar and syntax of the manuscript.

Compliance with ethical standards

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

References

1. Zimmermann MB (2012) The effects of iodine deficiency in pregnancy and infancy. Paediatr Perinat Epidemiol 26(supp 1):108–117
2. Zimmermann MB, Gizak M, Abbott K et al (2015) Iodine deficiency in pregnant women in Europe. Lancet Diabetes Endocrinol 3: 672–674
3. Clar C, Wu T, Liu G, Li P (2002) Iodized salt for iodine deficiency disorders. A systematic review. Endocrinol Metab Clin N Am 31(3):681–698
4. Vought R, London W (1967) Iodine intake, excretion and thyroidal accumulation in healthy subjects. J Clin Endocrinol Metab 27(7): 913–919
5. Zimmermann MB, Jooste PL, Pandav CS (2008) Iodine-deficiency disorders. Lancet 372(9645):1251–1262
6. Fisher DA, Oddie TH (1969) Thyroid iodine content and turnover in euthyroid subjects: validity of estimation of thyroid iodine accumulation from short-term clearance studies. J Clin Endocrinol Metab 29(5):721–727
7. Azizi F, Smyth P (2009) Breastfeeding and maternal and infant iodine nutrition. Clin Endocrinol 70(5):803–809
8. Bruhn JC, Franke AA (1983) Iodine in human milk. J Dairy Sci 66(6):1396–1398
9. Cavalieri RR (1997) Iodine metabolism and thyroid physiology: current concepts. Thyroid. 7(2):177–181
10. World Health Organization. United Nations Children's Fund & International Council for the Control of Iodine Deficiency Disorders (2007) Assessment of iodine deficiency disorders and monitoring their elimination. 3rd ed. WHO, Geneva
11. Glinoer D (1997) The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 18(3):404–433
12. Krassas G, Poppe K, Glinoer D (2010) Thyroid function and human reproductive health. Endocr Rev 31(5):702–755
13. Roti E, Fang SL, Emerson CH, Braverman LE (1981) Placental inner ring iodothyronine deiodination: a mechanism for decreased passage of T4 and T3 from mother to fetus. Trans Assoc Am Phys 94:183–189
14. Stulc J (1997) Placental transfer of inorganic ions and water. Physiol Rev 77:805–836
15. Di Cosmo C, Fanelli G, Tonacchera M et al (2006) The sodium-iodide symporter expression in placental tissue at different gestational age: an immunohistochemical study. Clin Endocrinol 65: 544–548
16. Bizhanova A, Kopp P (2009) Minireview: the sodium-iodide symporter NIS and pendrin in iodide homeostasis of the thyroid. Endocrinology 150:1084–1090
17. Glinoer D (2004) The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. Best Pract Res Clin Endocrinol Metab 18(2):133–152
18. Smyth PP (1999) Variation in iodine handling during normal pregnancy. Thyroid 9(7):637–642
19. Bath SC, Steer CD, Golding J et al (2013) Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). Lancet 382:331–337
20. Pop VJ, Kuijpens JL, van Baar AL et al (1999) Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol 50(2):149–155
21. Zimmermann MB, Andersson M (2012) Update on iodine status worldwide. Curr Opin Endocrinol Diabetes Obes 19(5):382–387
22. Hetzel B (1983) Iodine deficiency disorders (IDD) and their eradication. Clin Obstet Gynecol 322(8359):1126–1129
23. Glinoer D (2007) The importance of iodine nutrition during pregnancy. Public Health Nutr 10(12A):1542–1546
24. Haddow JE, Palomaki GE, Allan WC et al (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 341(8):549–555
25. Stagnaro-Green A (2011) Overt hyperthyroidism and hypothyroidism during pregnancy. ClinObstet Gynecol 54:478–487
26. Mannisto T, Mendola P, Grewal J et al (2013) Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. J Clin Endocrinol Metab 98:2725–2733
27. Karakosta P, Alegakis D, Georgiou V et al (2012) Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. J Clin Endocrinol Metab 97:4464–4447
28. Toulis KA, Stagnaro-Green A, Negro R (2014) Maternal subclinical hypothyroidsm and gestational diabetes mellitus: a meta-analysis. Endocr Pract 20(7):703–714
29. Jia M, Wu Y, Lin B et al (2019) Meta-analysis of the association between maternal subclinical hypothyroidism and gestational diabetes mellitus. J Gynaecol Obstet 144(3):239–247
30. Allan WC, Haddow JE, Palomaki GE et al (2000) Maternal thyroid deficiency and pregnancy complications: implications for population screening. J Med Screen 7:127–130
31. Benhadi N, Wiersinga WM, Reitsma JB et al (2009) Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. Eur J Endocrinol 160:985–991

32. Negro R, Schwartz A, Gismondi R et al (2010) Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab 95:E44–E48
33. Cleary-Goldman J, Malone FD, Lambert-Messerlian G et al (2008) Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol 112:85–92
34. Zoeller R, Rovet J (2004) Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J Neuroendocrinol 16(10):809–818
35. Glinoer D (2001) Pregnancy and iodine. Thyroid. 11(5):471–481
36. Hynes KL, Otahal P, Hay I et al (2013) Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. J Clin Endocrinol Metab 98(5):1954–1962
37. van Mil NH, Tiemeier H, Bongers-Schokking JJ et al (2012) Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children–3. J Nutr 142(12): 2167–2174
38. Ghassabian A, Steenweg-de Graaff J, Peeters RP et al (2014) Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area. BMJ Open 4:e005520
39. Oken E, Braverman LE, Platek D et al (2009) Neonatal thyroxine, maternal thyroid function, and child cognition. J Clin Endocrinol Metab 94:497–503
40. Murcia M, Rebagliato M, Iñiguez C et al (2011) Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. Am J Epidemiol 173:804–812
41. Vermiglio F, Lo Presti V, Moleti M et al (2004) Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 89(12): 6054–6060
42. Rebagliato M, Murcia M, Alvarez-Pedrerol M et al (2013) Iodine supplementation during pregnancy and infant neuropsychological development. INMA Mother and Child Cohort Study. Am J Epidemiol 177:944–953
43. Taylor PN, Okosieme OE, Dayan CM et al (2014) Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. Eur J Endocrinol 170(1):R1–R15
44. Azizi F, Kalani H, Kimiagar M et al (1995) Physical, neuromotor and intellectual impairment in non-cretinous schoolchildren with iodine deficiency. Int J Vitam Nutr Res 65(3):199–205
45. Oken E, Braverman LE, Platek D (2009) Neonatal thyroxin, maternal thyroid function, and child cognition. J Clin Endocrinol Metab 94:497–503
46. Abel MH, Caspersen IH, Meltzer HM et al (2017) Suboptimal maternal iodine intake is associated with impaired child neurodevelopment at 3 years of age in the Norwegian Mother and Child Cohort Study. J Nutr 147:1314–1324
47. Levie D, Korevaar TIM, Bath SC. et al. (2019) Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data. J Clin Endocrinol Metab
48. Gushurst CA, Mueller JA, Green JA et al (1984) Breast milk iodide: reassessment in the 1980s. Pediatrics. 73(3):354–357
49. Zimmermann MB (2008) Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. Am J Clin Nutr 89(2):668S–672S
50. Liesenkötter KP, Göpel W, Bogner U et al (1996) Earliest prevention of endemic goiter by iodine supplementation during pregnancy. Eur J Endocrinol 134(4):443–448
51. Pedersen K, Laurberg P, Iversen E et al (1993) Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. J Clin Endocrinol Metab. 77(4):1078–1083
52. Pastorelli AA, Stacchini P, Olivieri A (2015) Daily iodine intake and the impact of salt reduction on iodine prophylaxis in the Italian population. Eur J Clin Nutr 69(2):211–215
53. Dold S, Zimmermann MB, Jukic T et al (2018) Universal salt iodization provides sufficient dietary iodine to achieve adequate iodine nutrition during the first 1000 days: a cross-sectional multicenter study. J Nutr 148(4):587–598
54. Gowachirapant S, Winichagoon P, Wyss L et al (2009) Urinary iodine concentrations indicate iodine deficiency in pregnant Thai women but iodine sufficiency in their school-aged children. J Nutr 139:1169–1172
55. Wong EM, Sullivan KM, Perrine CG et al (2011) Comparison of median urinary iodine concentration as an indicator of iodine status among pregnant women, school-age children, and nonpregnant women. Food Nutr Bull 32: 206–212
56. Vandevijvere S, Mourri AB, Amsalkhir S et al (2012) Fortification of bread with iodized salt corrected iodine deficiency in school-aged children, but not in their mothers: a national cross-sectional survey in Belgium. Thyroid 22: 1046–1053
57. Delshad H, Touhidi M, Abdollahi Z et al (2016) Inadequate iodine nutrition of pregnant women in an area of iodine sufficiency. J Endocrinol Investig 39(7):755–762
58. Dahl L, Wik Markhus M, Sanchez PVR et al (2018) Iodine deficiency in a study population of Norwegian pregnant women—results from the little in Norway Study (LiN). Nutrients. 10(4):513
59. Yan YQ, Chen Z-P, Yang XM et al (2005) Attention to the hiding iodine deficiency in pregnant and lactating women after universal salt iodization: a multi-community study in China. J Endocrinol Investig 28(8):547–553
60. Caldwell KL, Makhmudov A, Ely E et al (2011) Iodine status of the US population, National Health and Nutrition Examination Survey, 2005–2006 and 2007–2008. Thyroid. 21(4):419–427
61. Pearce EN, Bazrafshan HR, He X et al (2004) Dietary iodine in pregnant women from the Boston, Massachusetts area. Thyroid. 14(4):327–328
62. Nazeri P, Mirmiran P, Shiva N et al (2015) Iodine nutrition status in lactating mothers residing in countries with mandatory and voluntary iodine fortification programs: an updated systematic review. Thyroid. 25(6):611–620
63. Bath SC, Rayman MP (2015) A review of the iodine status of UK pregnant women and its implications for the offspring. Environ Geochem Health 37(4):619–629
64. Condo D, Huyhn D, Anderson AJ et al (2017) Iodine status of pregnant women in South Australia after mandatory iodine fortification of bread and the recommendation for iodine supplementation. Mater Child Nutr 13(4):e12410
65. World Health Organisation. United Nations Children's Fund. International Council for the Control of Iodine Deficiency Disorders. (2007) Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. World Health Organisation; Geneva, Switzerland
66. Institute of Medicine, Food and Nutrition Board (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press
67. Markou K, Georgopoulos N, Kyriazopoulou V et al (2001) Iodine-induced hypothyroidism. Thyroid. 11(5):501–510
68. Secretariat W, Andersson M, De Benoist B et al (2007) Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the technical consultation. Public Health Nutr 10(12A): 1606–1611

69. Scientific Opinion on Dietary Reference Values for iodine. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) European Food Safety Authority (EFSA), Parma, Italy EF
70. Organization WH. Guideline (2014): fortification of food-grade salt with iodine for the prevention and control of iodine deficiency disorders
71. Harding KB, Pena-Rosas JP, Webster AC et al (2017) Iodine supplementation for women during the preconception, pregnancy and postpartum period. Cochrane Database Syst Rev 3:CD011761
72. Pharoah PO, Connolly KJ (1991) Effects of maternal iodine supplementation during pregnancy. Arch Dis Child 66:145–147
73. Pharoah PO, Connolly KJ (1987) A controlled trial of iodinated oil for the prevention of endemic cretinism: a long-term follow-up. Int J Epidemiol 16:68–73
74. Velasco I, Carreira M, Santiago P et al (2009) Effect of iodine prophylaxis during pregnancy on neurocognitive development of children during the first two years of life. J Clin Endocrinol Metab 94(9):3234–3241
75. Antonangeli L, Maccherini D, Cavaliere R et al (2002) Comparison of two different doses of iodide in the prevention of gestational goiter in marginal iodine deficiency: a longitudinal study. Eur J Endocrinol 147(1):29–34
76. Glinoer D, De Nayer P, Delange F et al (1995) A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. The Journal of Clinical Endocrinology & Metabolism 80(1):258–269
77. Nøhr SB, Laurberg P (2000) Opposite variations in maternal and neonatal thyroid function induced by iodine supplementation during pregnancy. The Journal of Clinical Endocrinology & Metabolism. 85(2):623–627
78. Berbel P, Mestre JL, Santamaría A et al (2009) Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. Thyroid. 19:511–519
79. Romano R, Jannini EA, Pepe M et al (1991) The effects of iodoprophylaxis on thyroid size during pregnancy. Am J Obstet Gynecol 164(2):482–485
80. Murcia M, Espada M, Julvez J et al (2018) Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: the INMA Mother and Child Cohort Study. J Epidemiol Community Health 72:216–222
81. Zhou SJ, Anderson AJ, Gibson RA et al (2013) Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. Am J Clin Nutr 98(5):1241–1254
82. Andersson M, De Benoist B, Delange F. et al. (2007) WHO Secretariat on behalf of the participants to the consultation. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2:1606–11
83. Gowachirapan S, Jaiswal N, Melse-boonstra A et al (2017) Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 5:853–863
84. Zimmermann MB (2007) The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. Thyroid. 17(9):829–835
85. Kirk AB, Kroll M, Dyke JV et al (2012) Perchlorate, iodine supplements, iodized salt and breast milk iodine content. Sci Total Environ 420:73–78
86. Mulrine HM, Skeaff SA, Ferguson EL et al (2010) Breast-milk iodine concentration declines over the first 6 months postpartum in iodine-deficient women. Am J Clin Nutr 92:849–856
87. Bouhouch RR, Bouhouch S, Cherkaoui M et al (2014) Direct iodine supplementation of infants versus supplementation of their breastfeeding mothers: a double-blind, randomized, placebo-controlled trial. Lancet Diabetes Endocrinol 2:197–209