Review

Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: A review

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ABSTRACT

Despite the introduction of salt iodization programmes as national measures to control iodine deficiency, several European countries are still suffering from mild iodine deficiency (MID). In iodine sufficient or mildly iodine deficient areas, iodine deficiency during pregnancy frequently appears in case the maternal thyroid gland cannot meet the demand for increasing production of thyroid hormones (TH) and its effect may be damaging for the neurodevelopment of the foetus. MID during pregnancy may lead to hypothyroxinaemia in the mother and/or elevated thyroid-stimulating hormone (TSH) levels in the foetus, and these conditions have been found to be related to mild and subclinical cognitive and psychomotor deficits in neonates, infants and children. The consequences depend upon the timing and severity of the hypothyroxinaemia. However, it needs to be noted that it is difficult to establish a direct link between maternal iodine deficiency and maternal hypothyroxinaemia, as well as between maternal iodine deficiency and elevated neonatal TSH levels at birth. Finally, some studies suggest that iodine supplementation from the first trimester until the end of pregnancy may decrease the risk of cognitive and psychomotor developmental delay in the offspring.

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Introduction

Iodine is an essential micronutrient for the production of the thyroid hormones (TH): thyroxin (T4) and tri-iodothyronine (T3).

These hormones play an important role in various functions of the human body, including the development of the central nervous system (CNS). According to the World Health Organization (WHO), 2.2 billion people are at risk of iodine deficiency worldwide, making it the leading cause of preventable brain damage [1]. Severe iodine deficiency during pregnancy may cause goitre, but also miscarriage, increased infant mortality [2] and congenital abnormalities like cretinism, which is an irreversible state of mental retardation

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appearing in combination with dwarfism, deaf-mutism and spasticity [3].

Severe endemic cretinism has mainly been observed in Central Africa and Asia. While in Europe severe iodine deficiency has been considered as a vanished problem, endemic goitre (with a prevalence of up to 90%) can still be found in several mountainous areas of Italy and Turkey [4,5]. Although the number of European countries in which iodine deficiency is a public health problem decreased from 23 in 2003 to 14 [6], it is a matter of concern that iodine deficiency has reappeared in countries whose previous iodine intake was sufficient, such as the UK [7]. Further, it is important to note that in countries in which iodized salt programmes supply sufficient iodine to the general population and pregnant women, weaning infants might still be at risk of inadequate iodine intakes [8]. Apart from being iodine deficient, some European countries have been shown to suffer from selenium deficiency, which may aggravate the consequences of mild iodine deficiency during pregnancy [9] because selenium deficiency may impair thyroid hormone metabolism [10]. Iodine deficiency associated with selenium deficiency has been shown to aggravate the risk of developing myxodematous cretinism in Africa [11]. Nevertheless, it is important to note that selenium deficiency also could have a protective effect against iodine deficiency [12]. The effects of iodine deficiency become more manifest during pregnancy, even in regions with borderline iodine supply, in case the thyroid gland cannot meet the demand for an increased production of TH. Even mild-to-moderate iodine deficiency (MID) in pregnancy may lead to isolated maternal hypothyroxinaemia, defined as a level of T4 below the normal range associated with a thyroid-stimulating hormone (TSH) level within the reference range [13–16]. In Europe, mild and subclinical cognitive and psychomotor deficits have been observed in neonates, infants and children, both in mildly iodine-deficient areas and even in iodine-sufficient areas when maternal T4 concentrations were in the low normal range during pregnancy [17–19].

Today, in several European countries, the iodine intake during pregnancy is considered to be insufficient [20–23] and iodine supplementation is recommended for pregnant women.

The WHO has recently increased the recommended iodine intake for pregnant women from 200 to 250 μg/day [24,25] and emphasized that periodic monitoring and adjustment of salt iodide concentrations is needed. Even in apparently iodine-sufficient regions in both Eastern and Western Europe, urinary iodine concentration (UIC) below 150 μg/day has been found in 50–92% and isolated hypothyroxinaemia has been detected in 4–10% of pregnant women [26–29]. Beside the prevalence of maternal isolated hypothyroxinaemia during pregnancy, the TSH screening in new-borns has been used to assess the severity of iodine deficiency during pregnancy [30]. In several European studies, elevated TSH values during the first days of life were found to be associated with suboptimal cognitive and psychomotor outcomes [31–34]. However, factors other than maternal iodine status may influence the TSH concentration, such as the TSH assay used [35], the timing of specimen collection [36–38] and the presence of several medical conditions in the mother [39–41].

The aim of this review was to investigate the importance of sufficient iodine intake during pregnancy by discussing the impact of MID during pregnancy on neurodevelopment of children. For this purpose, studies about thyroid function and iodine metabolism in pregnancy, transfer of TH and iodine from the mother to the foetus, the role of TH in foetal brain development, the neurodevelopmental outcomes of European children exposed to maternal hypothyroxinaemia and MID during pregnancy, and the effect of iodine or TH supplementation in pregnancy on cognitive and psychomotor outcomes were reviewed.
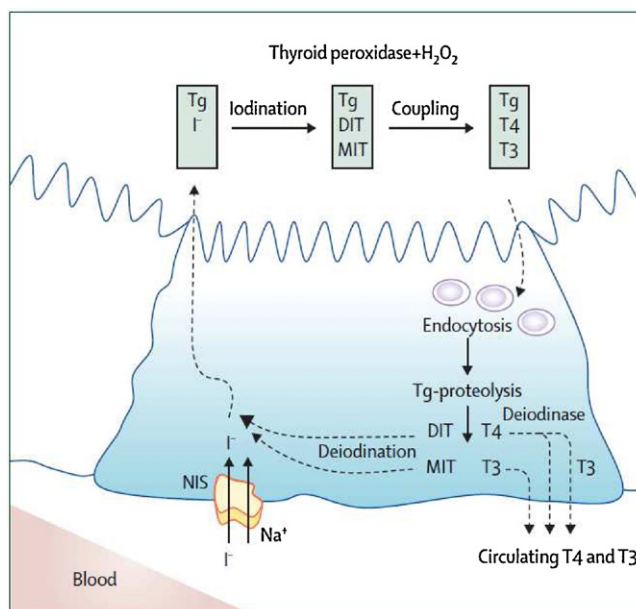

Fig. 1. Iodine pathway in the thyroid cell: Iodide (I⁻) is transported into the thyrocyte by the sodium/iodide symporter (NIS) at the basal membrane and migrates to the apical membrane. I⁻ is oxidised by the enzymes thyroperoxidase (TPO) and hydrogen peroxidase (H_2O_2) and attached to tyrosyl residues in thyroglobulin (Tg) to produce the hormone precursors iodotyrosine (MIT) and di-iodotyrosine (DIT). Residues then couple to form thyroxine (T4) and tri-iodothronine (T3) within the Tg molecule in the follicular lumen. Tg enters the cell by endocytosis and is digested. T4 and T3 are released into the circulation, and iodine on MIT and DIT is recycled within the thyrocyte.

Thyroid function during pregnancy

In the human body, 70–80% of iodine is located in the thyroid gland. Fig. 1 (adapted from Zimmermann et al., 2008 [42]) shows how iodine is used in the synthesis of TH. Iodine is oxidised in the follicular cells of the gland by a peroxidase and transformed into I2 [43]. I2 reacts with tyrosine of thyroglobulin (TG), which is the protein matrix on which TH are synthesized [44]. This reaction leads to the creation of monoidotyrosine (MIT) and diiodotyrosine (DIT) [43]. Association of two molecules of DIT forms T4 and association of one DIT with one MIT forms T3. The thyroid gland secretes mainly T4 molecules, while T3 is provided by type I deiodinase by outer ring deiodination of T4 in target cells [44]. The blood transport of thyroid hormones occurs with one of the following proteins: thyroxine-binding globulin (TBG), transthyretin or albumin [45].

TSH, which is synthesized in the anterior pituitary gland, controls and stimulates the production of TH. TSH is produced in response to a hypothalamic peptide TSH-releasing hormone (TRH). In order to maintain circulating TH levels within the required range, an increase of TH concentrations in blood (fT3 and fT4) results in a negative feedback on the production and release of TSH and TRH.

During pregnancy, hormonal changes and metabolic demands result in significant changes in thyroid function [46]. In pregnancy, there is an increased need for iodine supply [47] because of: (1) an increased production of TH, (2) an elevated renal clearance of iodine, and (3) the foetoplacental acquisition of maternal iodine and TH (Fig. 2) [48]

Increased production of TH

During the first half of pregnancy, concentrations of T4 and T3 increase significantly in order to maintain maternal euthyroidism. At the beginning of the second trimester T4 and T3 concentrations are 30–100% higher than before pregnancy [44,49]. This increased
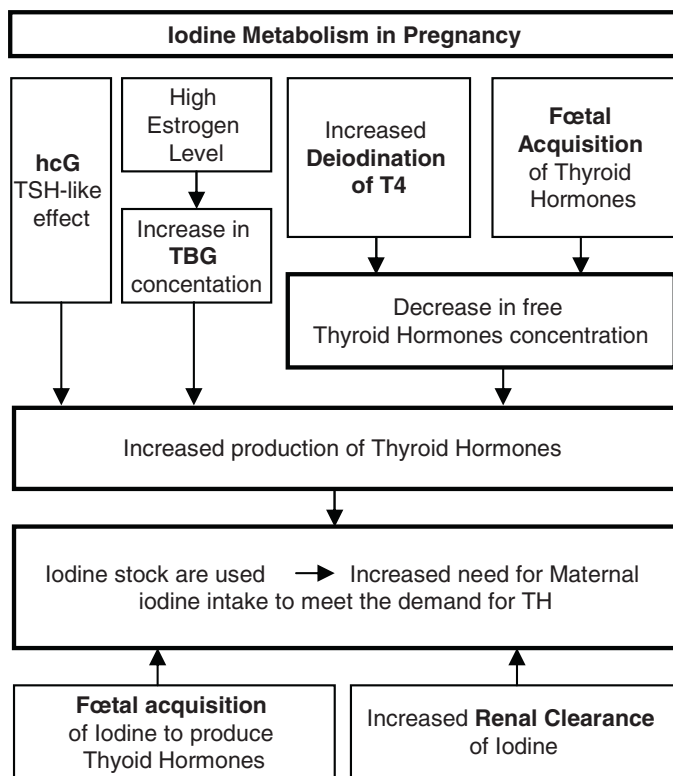
Fig. 2. Iodine metabolism in pregnancy.

production of TH can be explained by the following factors: (1) the increase in thyroxine-binding globulin TBG concentration, (2) the thyrotropic action of human chorionic gonadotropin (hCG), and (3) the increased activity of the enzyme type 3 iodothyronine deiodinase (D3).

There is an association between the rise of T4 and TBG [2,44]. TBG is the only protein of the three transport proteins which increases during pregnancy [2]. Its concentration is 2 or 3 times higher in pregnant women than among non-pregnant women [2]. The excess of TBG leads to an increase in the amount of circulating T4 [44] and to a decrease of T4 and T3 reserves in the thyroid gland of the mother [48]. The decrease in free hormone concentration leads to a rise of TSH concentration and TSH stimulates the thyroid gland in order to produce TH [2,48].

hCG may have a TSH-like effect because of the homologies between hCG and TSH molecules and their receptors [44,50,51]. During pregnancy, a high hCG concentration is associated with a decrease in serum TSH, which indicates an inverse relationship between these hormones [52,53,49,54]. Moreover, the hCG increase is associated with an elevation of TG. hCG may stimulate the production of TH by enhancing the production of TG [53]. TG is the protein matrix where TH are synthesized [44]. TG increases at the beginning of the first trimester and also during late gestation especially near term [55–59]. The thyrotropic action of hCG guarantees a maternal transfer to the foetus of TH in amounts necessary for foetal development, particularly during the stage of cerebral organogenesis which depends exclusively on TH supply from the mother [60]. This thyrotropic activity was documented in human pathologic conditions (hyperemesis gravidarum or trophoblastic tumours) and experimentally in rats [51,52]. In contrast, in non-pregnant women hCG administration had no effect on hypothalamic–pituitary–thyroid axis [61].

Another factor explaining the increased production of TH during pregnancy, to a lesser extent, is the foetal–placental activity of type 3 iodothyronine deiodinase (D3). D3 is a selenoenzyme inactivator

of TH, it turns T4 into reverse T3 (rT3) and T3 into diiodothyronine (T2) [62]. During pregnancy, the placenta D3 activity is important. In consequence, the maternal thyroid needs more supply of iodine in order to maintain a normal level of TH [44,63].

Elevated renal clearance of iodine

In addition to the increased production of TH, iodine losses in pregnancy are higher because of the increase in renal iodine clearance caused by the increase of glomerular filtration rate due to hyperoestrogenism [64–66]. Renal clearance of iodine starts to increase during the first week of gestation and persists until term [67–69].

Transfer of maternal iodine and TH to the foetus

The increased iodine requirement during pregnancy can also be explained by the transplacental transfer of TH from the mother to the foetus [2,70–72]. Thyroid development of the foetus starts at 10–12 weeks of gestation [73,74] and from the 18–20th week T4 is secreted by the foetal thyroid gland [2]. During this period, trans-placental transfer of iodine takes place from the mother to the foetal thyroid gland. Iodine transfer allows the foetal thyroid gland to produce its own TH [75–77].

Maternal TH supply and foetal brain development

For a long time, researchers assumed there is no transfer of maternal TH to the foetus. But more recently such a transfer has been demonstrated. First, maternal T4 is present in the coelomic fluid of the exocoelomic cavity of the foetus at the second month of gestation [78]. This maternal T4 is able to reach the embryo passing by the yolk sac, which is inside of exocoelomic cavity and connected with the digestive tract and circulatory system of the foetus [78]. Second, in foetus born without thyroid gland, T4 was detected in cord serum [79]. A study investigated TH in foetal blood by cordocentesis of normal foetus at 14 weeks of gestation or between 17th and 37th week of gestation. The conclusion of this study was that before the foetal hypothalamic–pituitary–thyroid system becomes operative, maternal T4 transfer is crucial for the foetus [80]. Finally, another study showed that one third of the amount of fT4 in extra-embryonic fluid is from maternal origin [71]. Transfer of maternal T4 varies during gestation [78,81] and during some period of gestation, a relationship between maternal and foetal level of T4 can be observed [82,83].

The foetal thyroid grows between 12 and 39 weeks of gestation. The most marked increase in the maternal thyroid size takes place during the second trimester when the foetal thyroid becomes functionally active [84].

At 10 weeks of gestation, nuclear T3 receptors can be identified in the foetal brain, showing a tenfold increase at week 16 [85,86]. TH used by the foetus is mainly T3. The supply of T3 is derived from foetal activity of type 2 and 3 iodothyronine deiodinase (D2 and D3) which takes place in order to transform maternal T4 in T3 [87]. This activity is modulated in case of iodine deficiency [88]. A level of maternal T4 within the normal range is needed to avoid T3 deficiency in the foetus. Indeed, early treatment of new-borns with congenital hypothyroidism born from mothers with sufficient T4 concentration showed good neurologic outcome results [89]. In contrast, normal values of maternal T3 associated with insufficient T4 showed no protective effect against foetal brain impairment [89]. An adequate maternal T4 supply is thus needed for the foetus in order to transform T4 into active T3 [71].

The maternal T4 transfer to the foetus is particularly important during early gestation because before 12–14 weeks of gestation the foetus is not able to produce its own T3 and T4 [48], while

TH hormones are essential for a normal brain development of the foetus [90]. Indeed, TH are involved in several important processes of brain development [91] through genomic [92–96] and non-genomic actions in glial cells and neurons [90]. TH plays a role in neural migration [97], neural differentiation [98], myelinisation [95,99–103], synaptogenesis [104] and neurotransmission [105–110]. TH are involved principally in the development of neural processes in the cerebral cortex, cochlea and basal ganglia [98]. Those areas are always affected in condition of endemic cretinism [111]. TH deficiency in the foetus may lead to a reduction of the number and distribution of dendritic spines in the auditory cortex [112]. A comparable effect was found in the pyramidal cells of the visual cortex [113,114]. Besides, in neocortex of therapeutically aborted foetuses from an iodine-deficient area, abnormal cytoarchitecture and heterotopic neurons were found. These alterations are similar to those found in rats exposed to maternal hypothyroxinaemia in early pregnancy [115–118]. This could indicate that brain foetal impairment could appear in iodine-sufficient areas. Insufficient supply of TH could have a long-term effect on the brain [119]. Indeed, in T4 treated adult rats a decrease in whole brain glucose use was observed after neonatal thyroidectomy [119].

Maternal hypothyroxinaemia and cognitive and psychomotor development during childhood

Several studies in Europe showed that isolated hypothyroxinaemia during pregnancy is associated with impaired cognitive development among children. These studies are summarized in Table 1.

A Dutch prospective cohort study showed that infants ($n = 220$) of women with hypothyroxinaemia at 12 weeks of gestation had significantly lower scores at the motor scale of Bayley Scales of Infant Development (BSID) at 10 months in comparison with infants of euthyroid women. No differences were seen when hypothyroxinaemia occurred at 32 weeks of gestation [17].

Another Dutch prospective cohort study showed that older infants (tested at 1 and 2 years; $n = 125$) of hypothyroxemic women at 12 weeks of gestation had delayed cognitive and motor development, as assessed by the BSID. In comparison with controls, they scored 10 points less on average on the mental scale and 8 points less on average on the motor scale at 2 years [18].

A Russian prospective cohort study showed that maternal hypothyroxinaemia at 5–9 weeks of gestation was associated with delayed cognitive performance of the offspring at 6 months, 9 months and 12 months [120].

A third Dutch prospective cohort study showed that neonates (aged 3 weeks) born from pregnant women with documented hypothyroxinaemia at 12 weeks of gestation had lower scores at the Neonatal Behavioural Assessment scale (NBAS) than control neonates, whereas hypothyroxinaemia occurring later in gestation had no effects on the NBAS score [19].

Another Dutch prospective cohort study evaluated the association between mild or severe hypothyroxinaemia during pregnancy and verbal and non-verbal development of children (aged 18, or 30 months). Mild hypothyroxinaemia was related to expressive language delay at ages of 18 and 30 months. Severe hypothyroxinaemia was shown to be a risk factor for expressive language delay at 18 and 30 months and across age [121].

A Portuguese prospective cohort study evaluated the development of 86 children, assessed by the BSID, at 12, 18 and 24 months and found that children born from mothers which had low fT4 concentration in the first trimester of pregnancy had lower motor scores at BSID than controls at 18 and 24 months [122].

A Spanish study evaluated 147 pregnant women and their child aged between 3 and 5 years. Hypothyroxinaemia in pregnant women at 37 weeks of gestation was related to significant lower performance of children on the general cognitive score, on the perceptual-manipulative score and the memory score evaluated with McCarthy Scale for Children Abilities (MSCA) [123].

Hypothyroxinaemia was defined in all of these studies as the 10th lowest percentile of value of fT4 of the study sample of pregnant women. These studies suggest that hypothyroxinaemia during pregnancy may affect cognitive development when appearing before or at 12 weeks of pregnancy. Moderate cognitive impairments have been observed in children from the age of 3 weeks up to 5 years. However, the low level of thyroid hormones observed in these studies cannot be directly attributed to iodine deficiency during pregnancy. Nevertheless, it must be noted that iodine deficiency is considered as the most common cause of hypothyroxinaemia [124]. The large Controlled Thyroid Screening Study recently failed to demonstrate improved neurocognitive outcome in 3-year-old children of mothers who were randomized to treatment of mild hypothyroxinaemia in pregnancy in comparison with children of untreated controls [125]. However, it is important to note that in this study treatment only started after 12 weeks of gestation.

Neonatal hyperthyrotropinaemia and cognitive and psychomotor development during childhood

Several studies in Europe evaluated the association between neonatal TSH level and the intellectual and psychomotor development of children. These studies are summarized in Table 2.

In Italy a case–control study assessed cognitive development with Wechsler scale of 9 children aged between 6 and 9 years with transient congenital hypothyroidism (TCH) or hyperthyrotrophinaemia (TNH) at birth and of 9 control children. Global and performance scores were significantly lower in the TCH/TNF than in control group [31].

A retrospective cohort study in Spain ($n = 178$) showed that children aged 3 years old with elevated TSH level at birth had lower scores at MSCA than those with normal TSH level, with significant differences in perceptual performance skills, memory development and general cognitive index [32].

Another Spanish retrospective cohort study evaluated the association between TSH level at birth and MSCA score among 178 children from a general population. They found that elevated TSH in cord blood was related to significant lower performance for general cognitive score and quantitative score of MSCA [33].

An Italian retrospective cohort study found that in a group of 102 preterm infants, a neonatal TSH value above 4.3 mU/L was related to a suboptimal neuromotor outcome at 18 months [34].

In contrast, one Italian prospective cohort study found no association between persistent subclinical hypothyroidism in children aged 4 up to 18 years ($n = 36$) and cognitive function [126].

The findings of all these studies suggest that abnormalities in thyroid function at birth, even when transient, might adversely affect intellectual or psychomotor development in early childhood. However, it is hard to claim that the observed impairments in cognitive functioning are a direct consequence of MID during gestation. An elevated TSH level at birth can be caused by several factors [35–41,127–131] and some of them affect both TSH levels and IQ in childhood [33,131–162]. Those factors are summarized in Table 3.

Maternal MID during pregnancy, iodine supplementation during pregnancy and cognitive and psychomotor development during childhood

Few studies in Europe have investigated the effect of iodine status and the effect of iodine supplementation of mildly

Table 1
Relationship between maternal hypothyroxinaemia and cognitive and psychomotor development during childhood: results from European prospective cohort studies.

Country	Subjects	Outcomes measured	Tools used	Main results	References
The Netherlands	Pregnant women (12 and 32 weeks of gestation) and their child tested (at 10 months of age), $n = 220$.	Cognitive and psychomotor performance of infants	BSID	Children of mothers with low fT4 levels at 12 weeks' gestation had significantly lower scores on the Bayley PDI compared to CC: -fT4 below 9.8 pmol/L (*t* test: mean difference: 14.1 (95% CI: 5.9–22.3) ($n = 11$ vs 209) -fT4 below 10.4 pmol/L (*t* test: mean difference: 7.4 (95% CI: 1.1–13.9) ($n = 22$ vs 198) At 32 weeks of gestation, no significant differences were found with CC. In the group of pregnant women with ft4 below 10.4 pmol/L, the lower the level of fT4, the lower was the PDI performance ($n = 22$, R: 0.46, $p = 0.03$).	Pop et al. [17]
The Netherlands	Pregnant women (hypothyroxinaemia fT4 < 10.4 pmol/L $n = 63$ vs CC $n = 62$) and their child at 1 and 2 years.	Intellectual and psychomotor development of children	BSID	Children of women with hypothyroxinaemia and TSH within the reference range (0.15–2.0 mU/L) at 12 weeks' gestation had: -At 1 years: A MDI which was 10 points lower ($p = 0.003$) and a PID which was 8 points lower ($p = 0.02$) than the CC. -At 2 years: A mental score which was 8 points lower ($p = 0.02$), and a motor score which was 10 points lower ($p = 0.005$) than CC. Decrease in maternal fT4 at 24 and 32 weeks' gestation did not affect performance of children.	Pop et al., [18]
Russia	Pregnant women (first trimester: fT4 < 10.95 ± 0.68 pmol/L $n = 13$ vs CC fT4 $n = 11$, third trimester: fT4 < 10.78 ± 1.31 pmol/L $n = 17$ vs CC fT4 $n = 18$) and their child at 6, 9 and 12 months.	Cognitive performance of progeny	Gnome method	An association was found between level of fT4 in the first trimester and the children's CMD at 6 months ($R = 0.684$, $p = 0.020$), 9 months ($R = 0.629$, $p = 0.038$), and 12 months ($R = 0.708$, $p = 0.014$). No association was found in the third trimester.	Kasatkina et al. [120]
The Netherlands	Pregnant women (12 weeks of gestation) with low fT4 (mean = 11.44 pmol/L, $n = 108$) or CC fT4 (mean = 17.0 pmol/L, $n = 96$) and their 3 weeks-old neonate. $N = 108$ (low fT4: below the 10th percentile of the sample/mean: 11.44 pmol/L vs 17 pmol/L) $n = 96$ (CC)	Behavioural performance of progeny	NBAS	CC neonates had better score at orientation cluster of NBAS than children born from mothers with low fT4 ($p = 0.042$)	Kooistra et al. [19]
The Netherlands	Pregnant women (fT4 < 11.76 pmol/L vs CC fT4) and their child ($n = 3659$) at 18 months ($n = 3411$) and 30 months ($n = 2819$)	Verbal (expressive vocabulary) and non-verbal performance of children	At 18 months: MCDI	Mild hypothyroxinaemia (fT4 < 11.76 pmol/L) was related to expressive language delay across age of 18 and 30 months (OR = 1.44; 95% CI = 1.09–1.91; $p = 0.010$)	Henrichs et al. [121]
			At 30 months: LDS and PARCA	Severe hypothyroxinaemia (fT4 < 10.96 pmol/L) is a risk factor for expressive language delay at 18 months (OR = 1.77; 95% CI: 1.10–2.84; $p = 0.018$), 30 months (OR = 1.78; 95% CI: 1.07–2.94; $p = 0.024$) and across age (OR = 1.80; 95% CI: 1.24–2.61; $p = 0.002$) and is a risk factor of non verbal cognitive delay at 30 months (OR = 2.03; 95% CI: 1.22–3.39; $p = 0.007$)	

Table 1 (Continued)

Country	Subjects	Outcomes measured	Tools used	Main results	References
Portugal	Pregnant women and their child tested at 12, 18 and 24 months $n = 86$	Cognitive and psychomotor outcomes of children	BSID	At 18 months and 24 months, children born from mothers with low fT4 (below 9 pg/mL) had significantly lower score at PDI than CC ($p < 0.05$). Children of mothers with fT4 levels below the 25th percentile (below 10 pg/ml) had a twofold higher risk of developmental delay.	Costeira et al. [122]
Spain	Pregnant women and their child tested between 3 and 5 years of age $n = 147$	Cognitive and psychomotor outcomes of children	MSCA	Hypothyroxinaemia (fT4 below 9.5 pmol/L) at 37 weeks of pregnancy was related to lower performance of children on the GCI score ($p < 0.01$), on the perceptual-manipulative score ($p < 0.001$) and memory score ($p < 0.05$).	Suárez-Rodríguez et al. [123]

BSID: Bayley Scales of Infant Development; CC: control children; CMD: coefficient of mental development; GCI: general cognitive index; LDS: Language Development Survey; MCDI: MacArthur Communicative Development Inventory; MDI: Mental Developmental Index; MSCA: McCarthy Scale for Children Abilities; NBAS: Neonatal Behavioural Assessment Scale; PARCA: Parent Report of Children's Abilities; PDI: Psychomotor Developmental Index; RR: relative risk; WISC-III: Wechsler Intelligent Scale for Children – third edition.

Table 2
Neonatal hyperthyrotropinaemia and cognitive and psychomotor development during childhood.

Country	Study design	Subjects	Tools used	Main results	References
Italy	Case–control study	Children (6–9 years) with TCH (elevated TSH and low T4 at birth and return to normal value 1–3 months after birth) or TNH (elevated TSH at birth and return to normal value 1–3 months after birth) ($n = 9$) and euthyroid children ($n = 9$)	WISC-R	Performance IQ and total IQ were significantly lower in TCH/TNH group than in CC. QIP: 89.2 ± 12.5 and 75 ± 8.5 ($p < 0.01$) QIT: 90.9 ± 14.2 and 78.3 ± 11.1 ($p < 0.05$)	Calaciura et al. [31]
Spain	Retrospective cohort study	Children of 40 months ($n = 61$): TNH (mean TSH: 3.90 ± 2.12 mU/L, TSH max value: 10 mU/L, 21.4% with TSH >5 mU/L) vs euthyroid children	MSCA	Score of TNH was significantly lower ($p < 0.005$) than score of CC for: perceptual performance skills (5.5), memory development (6.5) and GCI (9.8)	Riano et al. [32]
Spain	Retrospective cohort study	Boys of 4 years ($n = 178$) with cord blood TSH range 0.24–17 mU/L	MSCA	Elevated TSH at birth predicted lower performance at general cognitive score (-3.52; $p = 0.04$) and lower performance at executive function score (-3.15; $p = 0.05$). Lower scores were found for children with neonatal TSH level >4.19 mU/L in comparison with children with neonatal TSH level <2.05 mU/L for general cognitive score (-5.42; $p = 0.05$) and quantitative score (OR = 4.92; $p = 0.02$).	Freire et al. [33]
Italy	Retrospective cohort study	Preterm children (born between 26-32 week, $n = 102$) of 18 months	Griffiths Scales of Mental development	A strong correlation was found between elevated TSH values (>4.3 mU/L) and suboptimal motor score (OR = 14.6; (95% CI: 2.49–86.2)	Belcari et al. [34]
Italy	Prospective cohort study	Children of 4–18 years with TSH level between 4.2 mU/L and 10 mU/L ($n = 30$) and euthyroid children ($n = 36$)	Age appropriate IQ scale: 4–6 years: WPPSI 6–16 years: WISC-III Over 16 years: WAIS-R	Verbal score (99.1 ± 2.2), performance score (100.4 ± 1.9), and full-scale IQ (99.7 ± 1.9) were within the normal range and was not significantly different from scores of CC.	Cerbone et al. [126]

BSID: Bayley Scales of Infant Development; E: euthyroid; FTII: Fagan Test of Infant Intelligence (measure of recognition memory and speed processing: variable: percentage of novelty preference); GCI: general cognitive index. MSCA: McCarthy Scale for Children Abilities; TCH: transient congenital hypothyroidism; TNH: hyperthyrotropinaemia; WAIS-R: Wechsler Intelligent Scale for Children revised; WISC-III: Wechsler Intelligent Scale for Children – third edition; WPPSI: Wechsler Preschool and Primary Scale of Intelligence.

iodine deficient women during pregnancy on the cognitive and psychomotor development of the offspring. These studies are summarized in Table 4.

In an Italian cohort study, IQ score of children aged between 8 and 10 years from a MID region was significantly lower compared to those from a marginally sufficient area [163].

A Spanish cohort study showed that preschool children (aged 3 years) of pregnant women with urinary iodine excretion (UIE) lower than 200 μg/L at 12 weeks of gestation, had a significantly

Table 3
Factors explaining the increase associated or not with neurodeveloppement impairement.

Association of elevation of TSH and impaired neurodeveloppement	Elevation of TSH
In utero exposure to:	
Iodine excess [132–135]	TSH-receptor blocking antibodies from mothers with autoimmune thyroid disease [39–41]
Iodine containing drugs [136–139]	Antithyroid drugs (PTU, methimazole) [127,128]
Contrast agents [140]	
Organochlorides [33,141–143]	
Lithium [143–145]	
During neonatal period:	
Exposure to iodine-containing antiseptics [146–148]	Exposition to cold [129]
Perinatal anoxia [131,149,150]	Surgical hypothermia [130]
Multiple birth [151–153]	Delivery by forceps extraction [131]
Preterm birth [154–160]	
Low weight at birth [159,154,161,162]	
TSH testing:	
	Timing of blood sampling [36–38]
	TSH assay used [35]

PTU: propylthiouracil.

Table 4
Effect of MID and iodine supplementation during pregnancy on intellectual, cognitive and psychomotor functioning during childhood: results from European prospective cohort studies.

Country	Subjects	Tools used	Main results	References
Italy	Pregnant women from MID vs marginally sufficient areas and their child (8–10 years), n = 16	WISC-III	IQ score of child from MID region was significantly lower ($p < 0.05$) than IQ score of child from marginally sufficient area.	Vermiglio et al. [163]
Spain	Pregnant women and their child tested at 3 years. N = 61	MSCA	Significantly better score ($p < 0.005$) in perceptual performance skills (5.5 points), memory development (6.8) and GCI (9.8) when UIE >200 μg/L during pregnancy	Riano et al. [32]
Spain	Pregnant women who did/did not receive potassium iodine (300 μg/d) supplementation from the first trimester until the end of pregnancy and their child (3–18 months), n = 133	BSID	Children born from mothers who received iodine supplementation from the first trimester of pregnancy had higher score ($p = 0.02$) at PDI than children from mothers who did not receive supplementation	Velasco et al. [164]
Spain	Mild hypothyroxinaemic pregnant women (fT4 < 0.82 ng/dL) who did/did not receive potassium iodine (200 μg/d) supplementation from the first pregnancy visit (4–6 weeks or 12–14 weeks) until the end of lactation and their child (18 months), n = 34	Brunet–Lezine scale	No significant difference was observed between children born from mildly hypothyroxinaemic mothers and children born from mothers without hypothyroxinaemia	Berbel et al. [165]
Spain	Pregnant women (from 13 weeks of pregnancy) and their children (between 11 and 16 months of age), n = 691	BSID	Maternal UIE, consumption of iodized salt and foods with high iodine content was not associated with infant neurodevelopment	Murcia et al. [166]
			Iodine supplement intake during pregnancy of ≥150 μg/day was associated with a decrease of 5.5 points at PDI (only for girls) ($p = 0.001$) and with a 4-fold increase in the odds of a PDI < 85 for girls (95% CI: 1.4–11.4).	

BSID: Bayley Scales of Infant Development; MID: mild iodine deficiency; MSCA: McCarthy Scale for Children Abilities; PDI: Psychomotor Developmental Index; WISC-III: Wechsler Intelligence Scale for Children – third edition.

lower score at MSCA than children of pregnant women with a higher UIE [32].

In a Spanish cohort study, significantly higher motor scores of the BSID testing were found in young and older infants (aged 3–18 months) whose mother received iodine supplementation from the first trimester until the end of pregnancy (potassium iodide – 300 μg per day) in comparison with infants of mothers who did not receive supplementation [164]. On the other hand, in another Spanish cohort study, the IQ score by the Brunet–Lezine scale in older infants (aged 18 months) born from women with isolated hypothyroxinaemia diagnosed during the first 12–14 weeks of pregnancy and who received iodine supplementation (potassium iodide – 200 μg per day) from their first pregnancy visit onwards was not significantly different from the score of infants whose hypothyroxinaemic mothers were not supplemented [165].

Both studies were, however, not randomized, placebo-controlled trials.

Interestingly, a Spanish study even showed a negative impact of iodine supplementation on psychomotor development of girls at one year of age. No effect on psychomotor development was found for boys [166].

These studies suggest that mild iodine deficiency is associated with altered neurodevelopment of children from 3 to 10 years. A supplementation of potassium iodine of 200 μg per day seems to have no effect on infant neurodevelopment [165], whereas a supplementation of 300 μg per day, starting in the first trimester of pregnancy, may have a positive effect on infant psychomotor development [164]. Nevertheless, supplementation via iodine-containing multivitamins during pregnancy showed to affect psychomotor development of girls at one year of age [166].

There is a need for additional studies to understand the potential beneficial/harmful effect of iodine supplementation on child neurodevelopment.

Conclusion

Even in iodine-sufficient European countries pregnant women may be at risk of MID, because of the major physiological changes in thyroid function occurring during pregnancy leading to important losses of iodine and the need of much higher iodine supply. MID during pregnancy may, depending on the timing of occurrence and the severity of isolated maternal hypothyroxinaemia, affect the neurocognitive development of the offspring to some extent. Weak evidence is emerging that iodine supplementation of pregnant women from the first trimester until the end of pregnancy, even in mildly iodine-deficient pregnant women, is beneficial for neurocognitive development. Elevated neonatal TSH values, which may reflect exposure to iodine deficiency in utero when congenital hypothyroidism and other interfering conditions are excluded, might be prevented by adequate iodine supplementation during pregnancy. However it is difficult to establish a direct link between maternal iodine deficiency and maternal hypothyroxinaemia as well as between maternal iodine deficiency and elevated neonatal TSH levels at birth.

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