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Review shows that thyroid hormone substitution could benefit transient hypothyroxinaemia of prematurity but treatment strategies need to be clarified

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ABSTRACT

Aim

Thyroid hormones are crucial for fetal and neonatal brain development. This paper provides an overview of the normal role of thyroid hormones in fetal brain development and the pathophysiology of transient hypothyroxinaemia of prematurity (THOP). It also discusses the diagnostic and therapeutic controversies around THOP and looks at directions for future research.

Methods

We used the PubMed and Embase databases to identify papers published in English from 1969 to June 2018. This identified 20 papers about the impact of THOP on neurodevelopment and seven randomised controlled trials about therapeutic approaches from 1981-2016,

Results

THOP has been researched for more than three decades. The impact of temporarily low thyroxine levels, without any increase in pituitary-secreted thyroid-stimulating hormone at a critical timeframe in an infant's brain development, is still debated. Heterogeneity in THOP definitions, difficulties with thyroid hormone assessment, identifying patients at risk and a clear lack of sufficiently powered studies add to the current controversy. There are indications that thyroid hormone substitution might be useful in extremely low gestational age neonates with THOP.

Conclusion

Some preterm infants could benefit from THOP treatment, but more studies are needed to clarify further treatment strategies, including the optimal timing of initiation and duration.

KEY NOTES

- This review looked at the normal role of thyroid hormones in fetal brain development and the pathophysiology of transient hypothyroxinaemia of prematurity (THOP).
- We identified and analysed 20 papers about the impact of THOP on neurodevelopment and seven randomised controlled trials about therapeutic approaches from 1981-2016,
- Our conclusion was that thyroid hormone substitution could help extremely low gestational age neonates with THOP and preterm infants with supressed thyroid function.

KEY WORDS

Brain development, preterm birth, thyroid hormones, thyroxine, transient hypothyroxinaemia of prematurity

INTRODUCTION

In the last 50 years, spectacular advances have been made in the care of preterm born infants and these have led a more than ten-fold increase in survival rates, especially in extremely low gestational age neonates (ELGANs) born at less than 28 weeks of gestation. Unfortunately, long-term neurodevelopment is frequently affected in these infants, leading to

substantial emotional, psychological and economic burdens on the patients in their later life. These also affect their families and society (1).

Thyroid hormones are essential for fetal and infant neurodevelopment. In the brain, they play a pivotal role in migration and terminal differentiation of neurons and glia, which are processes that occur in specific time windows. During the first half of pregnancy, the fetus is completely dependent on their mother's thyroid hormone supply (2) and premature birth interrupts that supply.

Transient hypothyroxinaemia of prematurity (THOP) is an entity that occurs in preterm infants and is characterised by low circulating total and free thyroxine concentrations, without the expected increase in pituitary thyroid stimulating hormone secretion. The severity varies inversely with gestational age (2). It is not surprising that several studies have reported a strong association between THOP and neurodevelopmental impairments, since birth occurs at the crucial phase of in-utero progression of fetal thyroid hormone function, when the maternal thyroid hormone contribution is still substantial (3-5). However, a number of recent studies have been unable to confirm any association between THOP and neurodevelopmental impairment at pre-school and school age and in young adulthood (6-8). These results have questioned the relevance of this entity.

The aim of this review was to provide an overview of the current knowledge about the pathophysiology of THOP. We also wanted to explore the consequences of THOP on the infants' neurodevelopment in view of the normal development of the fetal thyroid function and the role of thyroid hormones in fetal brain development.

METHOD

We carried out a comprehensive review of papers published in English from 1969 to June 2018 using the PubMed and Embase databases and searched for various combinations of the words and terms: thyroid hormones, transient hypothyroxinaemia of prematurity, fetal brain development neurodevelopment and treatment. All the references were screened by title and abstract and we read the full text of the selected papers. The reference lists of the chosen papers were then screened to ensure that we included all the relevant electronic sources on this topic.

The search identified 20 papers about the impact of THOP on neurodevelopment and seven randomised controlled trials about therapeutic approaches published from 1981-2016. The randomised controlled trials comprised four about prophylactic therapy and three about substitution therapy (Table 1).

RESULTS

Thyroid hormones and fetal brain development

Thyroid hormones are important developmental hormones from an evolutionarily point of view. The process of amphibian metamorphosis is induced by thyroid hormones (9) and animal models have revealed the importance of thyroid hormones in mammalian development, especially for brain development (10).

Thyroid hormones do not play a role in very early neural developmental events, such as neural induction. However, they are involved in the regulation of later processes, such as neurogenesis, myelination, dendrite proliferation and synapse formation through activation of

numerous thyroid responsive genes (10). In the human fetus, the availability of cerebral triiodothyronine is mainly generated by local deiodination of thyroxine (11). Thyroid hormone receptors bind triiodothyronine with high affinity and regulate the expression of triiodothyronine responsive target genes. In general, the role of thyroid hormones is to accelerate the rate of gene expression during development, by working within specific time frames and with regional specificity. In addition, non-genomic actions of thyroxine and triiodothyronine have been demonstrated. For example, thyroxine acts through several signal transduction pathways on the expansion of progenitors in the neocortex and triiodothyronine acts on the maturation and plasticity of hippocampal pyramidal neurons (10).

The human fetus, and in particular the fetal brain, is completely dependent on the maternal thyroid hormone supply until mid gestation (Figure 1). Thyroid hormones of maternal origin have been detected in the embryonic cavity as early as 3.8 weeks after conception, (12). Human chorionic gonadotropin has the same alpha subunit as thyroid-stimulating hormone and exerts thyroid-stimulating hormone-like effects on the maternal thyroid gland, which leads to increased circulating maternal thyroid hormone levels. It has been hypothesised that these mechanisms ensure an adequate thyroid hormone supply to the fetus early in pregnancy (13). Total thyroxine concentrations in coelomic and amniotic fluids are about 100 times lower than in the maternal circulation. However, the markedly lower concentration of thyroid hormone binding globulins results in markedly higher free thyroxine than total thyroxine concentrations and these are capable of exerting biological effects on embryonic tissues (14).

By 12 weeks of gestation, the definitive haemochorial placenta is formed and placental thyroid hormone transfer occurs through active transcellular transport. Figure 1 gives an overview of the several factors that play a role in the trans-placental thyroid hormone

transport. So far, six different thyroid hormone transporters have been identified in human placentas (15). They include monocarboxylate transporters 8 and 10, which have the most specific thyroid hormone binding. Further research is being carried out on these, as well as L-type amino acid transporters 1 and 2 and organic anion transporting polypeptides 1A2 and 4A1, to determine their relative contributions to trans-placental thyroid hormone transport (13),(16). Iodothyronine deiodinases consist of three subtypes and these enzymes are responsible for thyroid hormone activation and inactivation: subtype one is iodothyronine deiodinase type 1, subtype two is iodothyronine deiodinase type 2 and subtype three is iodothyronine deiodinase type 3. Iodothyronine deiodinase types 2 and 3 are expressed in the human placenta (16, 17). It has been suggested that both enzymes play a role in the regulation of trans-placental passage of the thyroid hormones. Iodothyronine deiodinase type 3 has inner ring deiodinase activity and converts thyroxine to the inactive reverse triiodothyronine. It is the predominant placental deiodinase subtype and its activity levels are 200-times higher than iodothyronine deiodinase type 2 activity levels (18). In the first trimester, it is mainly localised in the apical membrane of the syncytiotrophoblasts and, therefore, it has been hypothesised that it plays a role in maternal thyroid hormone inactivation to protect the fetus against maternal thyroid hormone oversupply (17). This hypothesis has been supported by perfusion studies of isolated human term placenta lobules, which showed that most of presented maternal thyroxine was metabolised by placental Iodothyronine deiodinase type 3 and that inhibition of Iodothyronine deiodinase type 3 activity caused a 2,700-fold increase in thyroxine concentrations in the fetal circuit (19). Finally, it also contributed to the provision of iodide ions into the fetal circulation, which are used for thyroid hormone synthesis by the fetal thyroid gland (13). Iodothyronine deiodinase type 2 has outer ring deiodinase activity and converts the prohormone thyroxine to the active hormone triiodothyronine. Immunoreactivity studies carried out in the first trimester have demonstrated a predominant location in the villous cytothrophoblast layer, on the fetal aspect of chorionic villi, indicating that the thyroid hormone-activating enzymes played a role in supplying triiodothyronine to the developing fetus (17). One study showed

that increased placental iodothyronine deiodinase type 2 and decreased placental Iodothyronine deiodinase type 3 gene expressions were described in the placentas of pregnancies with vascular complications, ending in preterm birth. The preterm infants showed increased cord blood triiodothyronine levels. These findings suggest that the placentas displayed compensatory characteristics, in order to provide the fetus with sufficient triiodothyronine in hypoxic circumstances, when fetal development was under pressure (16). Finally, four different thyroid hormone-binding globulins have been identified in human placenta: transthyretin, albumin, alpha-1-antitrypsin and alpha-1-acid-glycoprotein (20). They may play a role in protecting thyroid hormones from metabolism during their transit through trophoblasts (20).

From mid-gestation, the fetal hypothalamic-pituitary-thyroid axis starts to function and this results in fetal thyroid hormone secretion. Maturation of the hypothalamic-pituitary-thyroid axis is progressive and only completed near term. Even ELGANs are able to respond to exogenous thyrotropin-releasing hormones by increasing thyroid-stimulating hormone levels. However, their thyroid-stimulating hormone response at birth, the thyroid-stimulating hormone surge, is blunted. Near term, circulating thyroid-stimulating hormone levels are relatively high. This is probably due to inactivation of thyroxine and triiodothyronine by iodothyronine deiodinase type 3, sulfation of thyroxine and triiodothyronine and high fetal thyrotropin-releasing hormone levels (2). The supply of maternal thyroid hormones remains substantial until the end of pregnancy, as demonstrated in term neonates with congenital hypothyroidism due to organification defects or thyroid agenesis (21). Figure 2 provides an overview of the interactions between the maternal thyroid hormone supply, fetal development of thyroid structures and actions on embryological brain development.

Even a short period of fetal thyroid hormone deficiency can affect brain development and the severity may be linked to the specific timing of onset and the duration of the deficiency.

Although the effects of severe congenital hypothyroidism can be largely prevented by the i*n utero* maternal supply, and by early postnatal thyroid hormone substitution therapy, embryological or fetal thyroid hormone deficiency cause neurodevelopmental deficits in the offspring, even when it is secondary to an inadequate maternal supply in early pregnancy (22). There is currently no evidence that maternal treatment for subclinical hypothyroidism results in better cognitive outcomes in their offspring. A randomised controlled trial with maternal treatment for sub-clinical hypothyroidism between eight and twenty weeks of gestation did not show significantly better cognitive outcomes in the offspring of mothers who received treatment until they were five years of age (23). Despite this, there is still speculation and discussions about whether it is ideal to initiate treatment before a baby is conceived, to ensure that there is an adequate thyroid hormone supply in the womb in early gestation, as during this period fetal brain development is completely dependent on maternal thyroid hormones (22).

Mechanisms of THOP

The aetiology of THOP is multifactorial (Figure 3). The sudden interruption of the trans-placental maternal thyroid hormone supply, together with immaturity of the hypothalamic-pituitary-thyroid axis and limited thyroid gland reserve, are important contributors and could explain why the severity of THOP has an inverse relation with gestational age. Indeed, ELGANs have limited thyroid hormone secretion, due to the immaturity of their hypothalamic-pituitary-thyroid axis and the fact that the maternal thyroid hormone supply is still crucial at the moment of birth (2). Persistent fetal thyroid hormone metabolism is another explanation. When the fetus is *in utero,* thyroid hormone metabolism is oriented towards neutralising the bioactivity of thyroxine and triiodothyronine by limited type 1 deiodinase activity in fetal tissues and the predominance of enzymatic sulfation of iodothyronines

(Figure 1). These mechanisms are reversed at around 30 weeks of gestation, in preparation of birth, resulting in increased fetal circulating triiodothyronine levels and decreased circulating reverse triiodothyronine and sulfated iodothyronine levels. In ELGANs, this transition has not yet been made and the fetal state may persist for weeks (2).

Major morbidities associated with preterm birth are respiratory distress and oxygen dependence, cranial ultrasound changes, persistent ductus arteriosus, necrotising enterocolitis and sepsis. They are most prevalent in infants under 30 weeks of gestation and almost twice as prevalent in ELGANs as in infants born between 28 and 30 weeks (24). The association of THOP with illness severity scores (25), respiratory distress syndrome (26), bacteraemia (26, 27), ventilator-associated pneumonia (27), persistent ductus arteriosus (27), necrotising enterocolitis (27), cerebral ultrasonography changes (25, 27) and oxygen dependence at 28 weeks (27) has been demonstrated in several studies. Non-thyroidal illness is a known condition in critically ill adults, in which a variety of illnesses cause a decrease in circulating triiodothyronine levels. In severe cases it also causes a decrease in circulating thyroxine levels, without an elevation in thyroid-stimulating hormone. During acute stress moments, there is a rapid decline in circulating triiodothyronine levels, whereas circulating reverse triiodothyronine concentrations rise acutely, with an absence of the nocturnal thyroid-stimulating hormone surge (28). Non-thyroidal illness is considered to be a possible adaptive response to reduced energy expenditure, with low triiodothyronine levels and an optimised capacity to kill bacteria due to increased Iodothyronine deiodinase type 3 activity in granulocytes (28). When critical illness is prolonged, the hypothalamic-pituitary-thyroid axis set point is down regulated and it seems that, despite the decrease in thyroid hormone production, peripheral tissues adapt by increasing thyroid hormone transporters, local activation of thyroid hormones and gene expression of the active receptor isoform (28). Prolonged critical illness is a recent phenomenon in the evolution of mankind and it is unclear whether this unnatural chronical stress response is the result of evolutionary

benefits. Since the paediatric population in general, and preterm infants in particular, should not be considered as small adults, we should also be cautious about extrapolating these findings to THOP. Although non-thyroidal illness can be one of the contributors to THOP, as suggested by Williams et al (27), hypothalamic-pituitary-thyroid set point regulation is not completely developed at birth, since the development of thyroid-stimulating hormone circadian rhythm only starts after the first month of life (29). Therefore, the relative contributions of hypothalamic-pituitary-thyroid immaturities and non-thyroidal illnesses to THOP remain unclear. Indeed, the most immature infants have the highest morbidity rates, as mentioned before. However, a study by Behme et al of late preterm infants, aged 34-36 weeks, could not find an association between THOP and neonatal morbidities, although 93% of the study population had a total thyroxine level that was below one standard error of the reference laboratory mean in the first week of life (30).

Finally, medication is often warranted in neonatal intensive care settings. Both dexamethasone (31) and dopamine (32) can suppress pituitary thyroid-stimulating hormone secretion and play a role in the development of THOP. In humans, glucocorticoid administration has been shown to decrease plasma thyroid-stimulating hormone levels and attenuate the pituitary thyroid-stimulating hormone response to thyrotropin-releasing hormone stimulation, together with a shift from reverse triiodothyronine over triiodothyronine formation (33). Dopamine acts on specific iodothyronine deiodinase type 2 receptors in the anterior pituitary and in the hypothalamic median eminence, localized outside the blood-brain barrier and inhibits the release of prolactin, growth hormone, thyroid-stimulating hormone and other pituitary hormones (32). Iodinated disinfectants also cause thyroid dysfunction, transient hypothyroidism and hyperthyrotropinaemia, because the excess of iodine supresses thyroid hormone synthesis by the thyroid gland (34).

Impact of THOP on infant neurodevelopment

Table 1 summarises the studies that have investigated the impact of THOP on infant neurodevelopment. The majority of these studies showed that the most persistent and lowest neonatal thyroid hormone levels were associated with impaired neurodevelopment at pre-school and school age (3-5, 35-45). Although the impaired neurodevelopment seen at school age in a Dutch study cohort was no longer present in young adulthood (8), there was an association between THOP and behavioural disturbances (46). Some studies could not show an association between THOP and impaired neurodevelopment, possibly due to heterogeneity in THOP definitions (6-8, 47, 48). Indeed, the definition of optimal ranges for circulating thyroid hormones in preterm infants related to gestational and postnatal age remains unclear. Moreover, circulating thyroid hormone levels do not reflect the thyroid hormone status at the cellular level and it is questionable at which threshold there is sufficient circulating thyroxine available to result in sufficient intracellular triiodothyronine for normal neuronal development. Moreover, difficulties in total and free thyroxine measurements are present in preterm infants and this adds to the complexity of this phenomenon. The golden standard method for free thyroxine determination is equilibrium dialysis, but this technique is expensive and labour intensive. Therefore, commercial kits are often used. However, these are often unreliable, because free thyroxine levels are overestimated in case of high thyroid hormone protein binding capacity and underestimated at low protein concentrations, which are often present in preterm and sick newborn infants. Two studies that used the equilibrium dialysis technique to determine thyroid hormone levels in preterm infants, described the depression of total thyroxine levels, but maintenance of free thyroxine levels in ELGANs during the second week of life (24, 34). On the other hand, displacement of total thyroxine from thyroid binding globulin by drugs such as heparin, metabolites and free fatty acids, leads also to increased free thyroxine levels and ELGANs are more likely to have conditions necessary for the displacement of protein-bound thyroxine (24).

To treat or not to treat?

Based on previous clinical findings, treatment regimens for THOP are controversial. Nevertheless, data from animal and clinical studies have shown the importance of having an adequate supply of thyroid hormones during critical moments of brain development. This is the case for most ELGANs, who are almost totally dependent on maternal thyroid hormone at the time of their birth (10, 22).

Therapeutic approaches for THOP can be divided into either substitution therapy or a prophylactic approach. Currently, there is no evidence for thyroid hormone substitution therapy in preterm infants with THOP. In 1984, Chowdhry et al studied 23 patients with THOP who were between 25-28 weeks of gestation and had a birth weight less than 1,250g. THOP was defined as serum total thyroxine levels ≤ 4µg/dL and thyroid-stimulating hormone levels ≤ 20IU/L. On day 15 of life the infants were randomised to either levothyroxine treatment (10µg/kg/d) or a placebo for seven weeks. There were no short-term beneficial effects of thyroxine treatment and sufficient neurodevelopmental data were lacking (49). One study of 60 ELGANs showed that levothyroxine treatment for free thyroxine levels of less than 0.8ng/dL at the end of the first week of life could reduce the incidence of cerebral palsy, when compared to a former cohort of 54 ELGANs who did not receive treatment (50). However, we must be careful with these results, because a historical control group was used and cerebral palsy rates have generally decreased over time. A randomised placebo controlled trial of 51 infants with a birth weight of less than 1,500g and THOP between two and four weeks of age could not show a neurodevelopmental benefit until a corrected age of three years. In that study THOP was defined as thyroid-stimulating hormone levels of less than 10µU/ml and free thyroxine levels of less than 0.8ng/dL (51).

No evidence for prophylactic thyroid hormone supplementation in preterm infants has been established either. Two studies started supplementation in the first 48 hours of life, but had different treatment regimens. However, both studies showed no reduction in neonatal mortality and morbidity or improvements in neurodevelopmental outcome in the thyroxine-supplemented group (52, 53). A study by Van Wassenaer et al produced notable *post hoc* results from a subgroup analysis (53). The authors studied 31 infants born at 25-26 weeks of gestation and found that the mean mental-development score in the thyroxine group was 18 points higher than the placebo group. In contrast, when they studied 125 infants born at 27-29 weeks of gestation, they found a trend towards a lower score in the thyroxine group than the placebo group (53). Another paper on the same cohort showed that even when the subjects reached 10 years of age, thyroxine supplementation was still associated with better school outcomes in infants born at less than 27 weeks of gestation and better motor outcome in those who were born at less than 28 weeks of gestation. The reverse was true for those who were born at 29 weeks of gestation (54). Adaptive mechanisms in brain iodothyronine deiodinase types 2 and 3 activity help supply sufficient free thyroxine and triiodothyronine to brain cells in case of scarcity of thyroid hormones (55). It has been hypothesised that these adaptive mechanisms are not fully developed in ELGANs, together with insufficient supplies of free thyroxine in those who have THOP (5). Important thyroid hormone-dependent processes may occur during this time frame and, therefore, thyroid hormone supplementation in these infants might be beneficial. With that in mind, several randomised placebo-controlled trials have been undertaken to study thyroid hormone supplementation in ELGANs. La Gamma et al investigated several supplementation regimens in 166 ELGANs to identify the optimal approach that resulted in increasing total thyroxine and free thyroxine levels without suppressing thyroid-stimulating hormone levels (34). The authors reported that a continuous supplement of 4µg/kg/d for 42 days resulted in elevated circulating total thyroxine levels, with only a modest suppression of thyroid-stimulating hormone, a decreased duration of mechanical ventilation and a decreased incidence of retinopathy of prematurity. Nevertheless, when they followed up 66% of the

infants at 36 months of corrected age, they could not show any benefit of total thyroxine supplementation, possibly due to insufficient power (56). In 2013, the TIPIT trial, which was a double blind randomised placebo controlled trial that recruited 153 ELGANs in the first five days of life, showed that thyroxine supplementation made no difference to the width of the subarachnoid space when it was measured by cranial ultrasound at 36 weeks of corrected gestational age (45). However, there was a significant correlation between low free thyroxine levels and the wider subarachnoid space. In a sub study of 45 patients, estimates of white-matter development using magnetic resonance imaging were not associated with the allocation of placebo or thyroid supplementation, but markers of poorly organised brain microstructure were associated with low plasma free thyroxine levels after birth (44). To date, no long-term outcome data from this study have been published.

DISCUSSION

Taken together, these findings together suggest that thyroid hormone substitution might be beneficial in ELGANs with THOP, because their brain development is still in a thyroid hormone sensitive time frame. However, the optimal moment when circulating thyroid hormone treatment should be started, and the duration of the treatment, remain unclear in terms of maximum benefit. From a theoretical point of view, it seems reasonable to select patients whose thyroid hormone levels are below the cord blood levels of infants of equivalent gestational age and not to keep the infants in a long-lasting hypothyroxinemic condition before intervention. However, further studies are warranted.

We also need to be aware of the possible side effects of treatment. The association between levothyroxine treatment and late-onset circulatory collapse has been reported in preterm infants (57). Adult studies have shown that levothyroxine monotherapy may induce acute adrenal insufficiency, since it increases the demand for cortisol as a consequence of

increased metabolism. This may also be true for preterm infants. However, the combination of thyroid and adrenal insufficiency may also be seen as a consequence of common backgrounds associated with extreme immaturity. Scott et al showed that combined low thyroxine and cortisol values were found in the sickest infants, who failed to improve their respiratory requirements. The authors had compared them with infants with so-called developmental hypopituitarism, whose conditions had improved or were at low levels across week one. As a result of their findings they suggested taking the relationship between cortisol and thyroid hormones into account in further prospective studies (58). Although thyroid hormone administration had no effect on cortisol levels in the La Gamma et al study (34), there are currently no data available about the effects of thyroid hormone supplementation in cases of corticosteroid treatment for preventing bronchopulmonary dysplasia. Studies of thyroid hormone supplementation in case of dopamine treatment are also lacking and, although dopamine is the first drug of choice in hypotension treatment in preterm infants, it is questionable whether alternative medication must be used.

A prophylactic randomised controlled trial by Vanhole et al focused on dynamic testing of the thyroid system by thyrotropin-releasing hormone administration in preterm infants. This showed that there was a brisk thyroid-stimulating hormone response, accompanied by a surge of circulating triiodothyronine in the placebo group, but not in the treated group. The results suggested a hypothalamic component in THOP (52). In infants with THOP, the thyroid-stimulating hormone response to the thyrotropin-releasing hormone stimulation test was comparable with that of euthyroid infants, but no data about the subsequent peripheral thyroid hormone response were available (59). Also in non-thyroidal illness, both animal and human clinical studies have demonstrated the ability of thyrotropin-releasing hormones to reactivate the thyroid axis (28). The immaturity of the hypothalamic-pituitary-thyroid axis in preterm infants, together with the ability of the end organs to respond to the stimulated

release of thyroid hormones, might suggest a role for thyrotropin-releasing hormone in the therapeutic approach of THOP. However, further studies are required.

This review had limitations, because only English search terms were used. Nevertheless, by focussing on the heterogeneity in the THOP definitions, the difficulties with thyroid hormone assessment and the lack of sufficiently powered studies, it demonstrated several factors that added to the current controversy. These insights might help to set out directions for further research.

CONCLUSION

Thyroid hormones are essential for brain development. In THOP, circulatory thyroid hormones are temporarily low and the severity is inversely related to gestational age. It is unclear at which level circulating thyroid hormones affect brain development, but thyroid hormone-sensitive developmental processes occur during a specific time frame. The correct assessment of circulating total and free thyroxine levels in preterm infants, due to low protein concentrations and competition with other substances for protein binding, also contributes to the complexity and controversies of this phenomenon. Nevertheless, limited data suggest that there might be a role for a therapeutic approach in ELGANs with low free thyroxine levels. Further work is needed to identify when treatment may be beneficial, based on the optimum threshold of circulating thyroid hormones. In addition, further treatment strategies still need to be clarified, including the optimal moment to start treatment and the ideal treatment duration. Data about further suppression of the thyroid function are lacking, for example when certain medication, such as corticosteroids and dopamine, are used. Further studies are required to investigate the role of thyroid hormone supplementation therapy in these conditions.

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ABBREVIATIONS

ELGANs; extremely low gestational age neonates; THOP; transient hypothyroxinaemia of prematurity

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1: Impact of transient hypothyroxinaemia of prematurity (THOP) on infant development

Author	Year	Method	Study Population	n	Definition of THOP	Outcome parameter	Outcome results
Hadeed et al (47)	1981	Observational case-control study	GA: 28 - 35 weeks	39	Cord blood T4 levels < 6.5 µg/dL	Neurodevelopment at 12 months of corrected age (Gesell Development test)	No differences in neurodevelopment between patients with and without THOP
De Vries et al (35)	1986	Observational case-control study	GA ≤ 31 weeks and birth weight ≤ 1,500g, compared to term infants	33	T4 levels < 4.67 µg/dL (cut-off point for preterm infants in neonatal screening programmes)	Nerve conduction velocity (ulnar and posterior tibialis nerve)	Prolonged hypothyroxinaemia (d21) was associated with a delay in nerve conduction velocity
Lucas et al (36)	1988	Observational case-control study	Preterm infants, birth weight < 1,850g	280	T3 levels divided in 3 categories: < 19.5 ng/dL; 19.5-39.1 ng/dL; > 39,1 ng/dL	Neurodevelopment at 18 months (Bayley Scale of Infant Development – 2nd Edition)	T3 levels < 19,5 ng/dL were associated with 8.3 and 7.4 point disadvantages in Bayley mental and motor scales and 8.6 point disadvantage on the academic scale of Developmental Profile II, after adjustment for antenatal and neonatal factors.
Karna et al (48)	1991	Observational case-control study	GA ≤ 33 weeks	16	free T4 levels < 0.8 ng/dL	Neurodevelopment at mean age of 4.,6 years (Stanford-Binet testing)	No significant difference between infants with THOP and without THOP in motor development, hearing, language or physical growth.
Meijer et al (37)	1992	Observational longitudinal cohort study	GA < 32 weeks and/or birth weight < 1,500g	563	T4 levels expressed as standard deviation of the mean of the total screened population (Dutch national screening for congenital hypothyroidism)	Neurodevelopment at the corrected age of 2 years (Gesell test adapted for Dutch children (revised Van Wiechen test)	Significant association between low neonatal T4 scores and a negative score on the three milestones of neurodevelopment
Den Ouden et al (38)	1996	Observational longitudinal cohort study	GA < 32 weeks and/or birth weight < 1,500g	640	T4 levels expressed as standard deviation of the mean of the total screened population (Dutch national screening for congenital hypothyroidism)	Neurodevelopment at the age of 5 years (neurologic examination according to Touwen, Denver Developmental Screening Test, speech and language assessment validated for Dutch children) School performance at	Both neurological dysfunction at 5 years and school failure at 9 years were significantly related to lower neonatal T4 levels, also after adjustment for other perinatal factors

						9 years (parental questionnaire)	
Lucas et al (4)	1996	Observational case-control study	Preterm infants, birth weight < 1,850g	236	T3 levels divided in 3 categories: < 19,5 ng/dL; 19,5-39,1 ng/dL; > 39,1 ng/dL	IQ at age of 7.5 - 8 years (abbreviated version of the revised anglicised Weschler intelligence scales for children)	Neonatal T3 levels < 19.5 ng/dL: substantial deficits in IQ scores, even after adjustment for perinatal factors
Reuss et al (3)	1996	Observational case-control study	GA ≤ 33 weeks and birth weight ≤ 2,000g	400	T4 levels < - 2.6 SD of the mean of the total screened population	Neurodevelopment at the age of 2 years (Bayley Scale of Infant Development – 2nd edition)	After adjustment for GA and multiple prenatal, perinatal, and early and late neonatal variables, severe hypothyroxinaemia was still associated with an increased risk of disabling cerebral palsy (odds ratio, 4.4; 95% confidence interval, 1.0 to 18.6) and a reduction of nearly 7 points (95% confidence interval, 0.3 to 13.2 points) in the mental-development score.
Leviton et al (39)	1999	Observational case-control study	Preterm infants with birth weight between 500 – 1,500g	1,414	T4 levels in first week of life below P25 among all infants in this sample	Echolucency in the cerebral white matter (ultrasound findings)	After adjustment for confounders, infants with THOP had twice the risk of echolucency as their peers with higher T4 levels
van Wassenaer et al (5)	2002	Observational case-control study	GA 25 - 30 weeks	79	Free T4 levels < P25 of the average levels of the study group	Neurodevelopment at the age of 2 years (Bayley Scale of Infant Development– 2nd edition)	Low free T4 levels during the first 4 weeks of life are associated with worse neurodevelopmental outcome at 2 and 5 years
Rovet et al (40)	2008	Observational case-control study	2 study cohorts: GA 29 - 35 weeks and GA 23 - 35 weeks	1st cohort: 47 2nd cohort: 67	Absolute values of TSH, free T4 and total T3	Visual attention at 3 months, visual abilities at 6 months and visuospatial abilities at 12 and 18 months	Reduced visual attention at 3 months of age, poor contrast sensitivity and colour vision at 6 months of age and weak visuomotor skills at 12 and 18 months of age were predicted by low thyroid hormone levels between 2 weeks of life

							and term age. Also ROP severity was associated with early thyroid hormone insufficiency.
Delahunty et al (42)	2010	Observational case-control study	GA ≤ 34 weeks	442	T4 levels ≤ P10 on d7, 14 or 28 corrected for GA	Neurodevelopment at 5.5 years of corrected age (McCarthy scale, adjusted for 26 influences on neurodevelopment)	Hypothyroxinemic infants scored significantly lower than euthyroid infants on the general cognitive and verbal scales
Simic et al (41)	2010	Observational case-control study	GA 23 - 35 weeks	67	Absolute values of TSH, free T4 and total T3	Visual acuity, contrast sensitivity and colour vision at 6 moths of corrected age	Reduced contrast sensitivity and slow blue-yellow and red-green colour vision processing were associated with low thyroid hormone levels, low GA and PDA
Ares et al (43)	2011	Observational case-control study	GA 28 - 36 weeks	46	Absolute values of total and free T4	General cognitive, verbal and memory indexes at 4 years of age	Higher T4 levels were associated with higher developmental indexes and lower T4 levels were associated with lower developmental indexes
Dilli et al (6)	2012	Observational case-control study	Birth weight ≤ 1,500g and GA ≤ 32 weeks	56	T4 levels < P25 with normal TSH levels in 1st week of life	Neurodevelopmentat 18-24 months of corrected age (Bayley Scale of Infant Development– 2nd edition)	No associations between THOP and impaired neurodevelopment
Ng et al (45)	2013	Multiple-centre double-blind randomised placebo controlled trial	GA < 28 weeks	118	Absolute values of TSH and free T4	Multiple-centre double-blind randomised placebo controlled trial: levothyroxine supplementation versus placebo. Primary outcome: brain size assessed by the width of the subarachnoid space	In general, supplementing therapy had no apparent effect on brain size. The lower the mean fT4 levels, the wider the subarachnoid space
Ng et al (44)	2014	Multiple-centre double-blind randomised placebo controlled trial	GA < 28 weeks	45	Absolute values of TSH and free T4	Multiple-centre double-blind randomised placebo controlled trial: levothyroxine supplementation versus placebo. Brain MRI using diffusion tensor imaging	No association of DTI variables with allocation of placebo or thyroid supplementation. Markers of poorly organised brain microstructure were associated with low plasma free T4 concentrations after birth

Scratch et al (7)	2014	Observational case-control study	GA < 30 weeks	83	Area under the curve calculation of repeated measures of fT4 in the first 6 weeks of life	Neuropsychological assessment at 7 years and brain MRI	Impaired neurodevelopment was associated with higher fT4 levels instead of lower fT4 levels
Hollanders et al (8)	2015	Observational longitudinal cohort study	GA < 32 weeks and/or birth weight < 1,500g	398	T4 levels < -3SD	Neurodevelopment at 19 years (digital Multicultural Capacities Test - Intermediate Level and a revised version of Touwen's examination of minor neurological dysfunction)	No association between THOP and neurodevelopmental outcome at age 19 years were found
Hollanders et al (46)	2016	Observational longitudinal cohort study	GA < 32 weeks and/or birth weight < 1,500g	468	T4 levels < -3SD	Behavior problems at 19 years (Young Adult Self Report and the Young Adult Behavioral Checklist for parents)	THOP was associated with more internalising and total problem behaviour at age 19 years

n, number of patients; THOP, transient hypothyroxinaemia of prematurity; GA, gestational age; T4, total thyroxine; T3, total triiodothyronine; IQ, intelligence quotient; fT4, free thyroxine; TSH, thyroid-hormone stimulating hormone; ROP, retinopathy of prematurity; PDA, patent ductus arteriosus; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging; SD, standard deviation

Figure legends

Figure 1: Interactions between the maternal, placental and fetal compartment to provide the fetus with sufficient thyroid hormones for the development and induction of fetal thyroid hormone metabolism

A. Maternal thyroid hormone secretion is increased under impulse of placental secreted human chorionic gonadotrophin.
B. Maternal thyroid hormones are transferred through the placenta by means of six different thyroid hormone transporters: monocarboxylate transporters 8 and 10, L-type amino acid transporters 1 and 2, organic anion transporting polypeptides 1A2 and 4A1. Deiodinases type 2 and type 3 are present in the placenta and play a role in tight regulation of thyroid hormone transfer towards the fetus. Four different thyroid-hormone-binding proteins are present in the placenta: transthyretin, albumin, alpha-1-antitrypsin, alpha-1-acid-glycoprotein.
C. In the first half of pregnancy, only maternal thyroid hormones are present in the fetal compartment. Brain and thyroid structures are developed and from mid-gestation there is fetal thyroid hormone secretion under impulse of hypothalamic-pituitary-thyroid axis stimulation. Thyroid hormones are transported to target tissues through several thyroid hormone transporters. In the first and second trimester, further activation of the active hormone T3 is limited by predominance of enzymatic sulfation through sulfotransferase activity and limited deiodinase type 1 activity. In the third trimester, in preparation of birth, these mechanisms are reversed.

TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone; T4, thyroxine; T3, triiodothyronine; rT3, reversed triiodothyronine; T2, diiodothyronine; D1, type 1 deiodinase (activating and inactivating properties); D2, type 2 deiodinase (activating properties); D3, type 3 deiodinase (inactivating properties); MCT,

monocarboxylate transporter; LAT, L-type amino acid transporter; OATP, organic anion transporting polypeptide; TR, thyroid hormone receptor.

Image adapted from Forhead (60).

Figure 2: Interactions between maternal thyroid hormone supply, fetal development of thyroid structures and actions on embryological brain development

A. Embryological and fetal development of brain structures
B. Embryological and fetal formation and maturation of thyroid hormone system structures
C. Until mid-gestation, the fetus is completely dependent on the maternal thyroid hormone supply. Thereafter, the fetal thyroid system starts to work, but it is only after birth that the infants' thyroid system functions are completely autonomously.

D2, type 2 deiodinase; T3, triiodothyronine

Image adapted from Bernal (10) .

Figure 3: Multifactorial aetiology of transient hypothyroxinaemia of prematurity