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Evolution of circulating thyroid hormone levels in preterm infants during the first week of life: perinatal influences and impact on neurodevelopment

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Abstract

Background: For several decades, transient hypothyroxinemia of prematurity (THOP) has been a topic of debate. The pathophysiology is incompletely understood and consensus on the therapeutic approach is lacking. This study aimed at gaining a better insight into the pathogenesis by studying the trends in thyroid hormone (TH) levels during the first week of life.

Methods: This single-center prospective observational study analyzed the plasma levels of total thyroxine (T4) and free thyroxine (fT4), total triiodothyronine (T3), thyroid-stimulating hormone (TSH) and T4-binding globulin (TBG) in cord blood and at the end of the first week of life in 120 preterm infants (gestational age [GA] <37 weeks). The change over time was calculated (delta, Δ). The impact of perinatal and subsequently postnatal variables on Δ was studied by hierarchical multiple regression. The impact of Δ on the neurodevelopmental outcome at the corrected ages of 9 and 24 months, measured by the Bayley Scales of Infant Development (BSID)-II, was assessed by logistic regression.

Results: ΔfT4 levels were negatively affected by GA and use of dopamine, whereas only GA was associated with low ΔT3 levels. Negative ΔfT4 levels were present in 75% of the extremely low-for-gestational-age infants, whereas 23.5% had a negative ΔT3 level. There was an increased risk for an abnormal mental developmental score (<85) with decreasing ΔT3 at 9 months, corrected age, but not at 24 months.

Conclusions: A negative evolution in circulating TH levels is principally an immaturity phenomenon, whereas dopamine can further suppress the hypothalamic-pituitary-thyroid axis. There is at least a temporary negative effect of this evolution on the infants' neurodevelopment.

Keywords: neurodevelopment; preterm birth; thyroid hormones; transient hypothyroxinemia of prematurity.

Introduction

Thyroid hormone (TH) is a frequently used term for thyroxine (T4) and triiodothyronine (T3). THs are key-players in fetal brain development [1]. Until mid-gestation, the fetus is completely dependent on maternal TH supply [2]. Then, the fetal thyroid system starts to function, but maternal transplacental TH transfer remains present until birth [2]. Preterm infants often present with transient hypothyroxinemia of prematurity (THOP), characterized by temporary low circulating TH levels without increased pituitary-secreted thyroid-stimulating hormone (TSH) levels [2]. THOP appears to be an important contributor to later disabilities, although data remain conflicting. This is partly explained by heterogeneity in THOP definitions [3]. Moreover, optimal ranges of circulating THs for organ maturation, according to specific gestational and postnatal ages, remain unclear [4].

As gestation progresses, fetal circulating TH levels increase [2]. Therefore, we hypothesized that a postnatal decrease in circulating TH levels reflects TH system immaturity and represents THOP. By studying THOP with this approach, the aim was to identify peri- and postnatal risk factors for the development of THOP and to assess the neurodevelopmental impact of impaired thyroid function.

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Materials and methods

Patient selection

This study was part of a larger single-center prospective observational study (September 2011–March 2014) in a tertiary-care hospital. Mothers at risk of preterm delivery and mothers with uncomplicated term delivery were included after obtaining written informed consent. Pregnancies complicated with fetal chromosomal defects and major congenital malformations such as cardiopathies, cerebral malformations and malformations of the gastrointestinal tract were excluded. For the present study, preterm-born infants (gestational age [GA] <37 weeks) were included. Relevant clinical data were collected as follows: maternal age, parity, maternal education level, tobacco use, course of betamethasone, mode of delivery, GA, birth weight, presence of intrauterine growth restriction (IUGR) and Clinical Risk Index for Babies (CRIB) score reflecting severity of illness in preterm infants [5], neonatal mortality, presence of invasive ventilation, patent ductus arteriosus (PDA), sepsis (positive blood culture) and dopamine and hydrocortisone use during the first week of life, presence of necrotizing enterocolitis (NEC), cranial ultrasound abnormalities, retinopathy of prematurity (ROP) with laser therapy, bronchopulmonary dysplasia (BPD, defined as O2 and/or ventilation need at 36 weeks postmenstrual age) and TH supplementation after the second sample was taken. TH supplementation (levothyroxine 10 µg/kg) for 14 days was initiated when free thyroxine (fT4) levels were below 0.8 ng/dL on time 2 (t2), according to the treatment regimen of the unit.

Sample collection

At delivery (time 1 [t1]), fetal cord blood plasma samples were collected, immediately centrifuged and stored at –20 °C. During the first week of life (range day 3–8) (t2), plasma TH levels were determined in the context of clinical care. Blood samples were primarily taken through an arterial line, or by venipuncture when no arterial line was available.

Blood analysis

TSH, T4, fT4, T3 and T4-binding globulin (TBG) were determined on all samples. Assays used were as follows: sandwich immunoassay with electrochemiluminescence (ECL), Hitachi/Roche-Modular E (Hitachi, Tokyo, Japan; Roche, Basel, Switzerland) for TSH; competitive immunoassay with ECL, Hitachi/Roche-Modular E (Hitachi, Tokyo, Japan; Roche, Basel, Switzerland) for fT4 and T3; RIA-gnost TBG kit (CISBIO, Paris, France).

Evolution of thyroid hormone function

The evolution of the peripheral thyroid function was calculated as follows: delta (Δ)T4 = $T4_{t2}$–$T4_{t1}$; ΔfT4 = $fT4_{t2}$–$fT4_{t1}$; ΔT3 = $T3_{t2}$–$T3_{t1}$. The impact of perinatal and subsequently postnatal variables on the Δs was studied by hierarchical multiple regression. Due to single-sample limitations in studying TSH dynamics, i.e. circulating TSH is both affected by pulsatile, circadian and ultradian variation, making single measurements less representative, ΔTSH levels were not used for further assessment.

Follow-up data collection

Neurodevelopmental follow-up at the corrected ages of 9 and 24 months was assessed by the Bayley Scales of Infant Development type II (BSID-II). Due to policy changes in the department at the end of the study, the BSID type III was used. The results were converted to BSID-II scores by the use of a validated conversion factor [6].

The BSID-II score was dichotomized in two different ways: cut-off values of 85 (moderately and severely disturbed vs. normal development) and 70 (severely disturbed vs. normal and moderately disturbed development).

Statistical analysis

Hierarchical multiple regression was used to study the effect of the following *a priori* defined perinatal variables on ΔT4, ΔfT4 and ΔT3, respectively: GA, mode of delivery, prenatal administration of betamethasone, presence of IUGR, maternal body mass index (BMI), tobacco use and CRIB score. Subsequently, the following *a priori* defined postnatal variables were added to the model: presence of invasive ventilation, PDA, sepsis, and the use of dopamine and hydrocortisone at the moment of the second sample. Correlations between ΔfT4 and ΔT3 were calculated by Spearman's rho test. Statistical analyses were performed using IBM SPSS Statistics (IBM, NY, USA).

Logistic regression models were used for data analysis of the follow-up data. The BSID-II score was analyzed as a binary variable. The interaction between Δ and time was modeled and estimated separately at both time points. In the absence of evidence for an interaction between Δ and time, the overall effect should be interpreted. In the presence of evidence for such an interaction, the effects at each time point should be interpreted. The results of the effect of Δ on the BSID-II score were expressed by odds ratios (ORs) with 95% confidence intervals (CIs). An OR >1 indicated an increased probability of abnormality as the predictor (Δ) increases. An OR <1 indicated lower probability of abnormality as Δ increases. Estimation was based on generalized estimating equations, to account for data clustering due to the presence of longitudinal data and twin pregnancies. Correction for possible confounders was performed by including these variables in the multivariable model (treatment, GA, intracranial lesion, BPD, ROP and sepsis). Variables were included as confounders when, in univariable analysis, a link was shown with both the outcome (BSID-II score) and the predictor of interest (Δ) ($p \leq 0.1$). No correction for multiplicity was applied, and the study should be considered exploratory and the results as hypothesis-generating. Analyses were performed using the SAS software (version 9.4 of the SAS System for Windows, Cary, NC, USA).

Data were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Statistical significance was assumed for a two-sided p-value ≤0.05.

Ethical approval

The research related to human use has complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration. It was approved by the local Ethical Committee (S53423) of the University Hospitals Leuven and registered at Clinicaltrials.gov (NCT01466023).

Results

Patient characteristics

The patient selection flow chart is shown in Figure 1. Patient characteristics are summarized in Table 1.

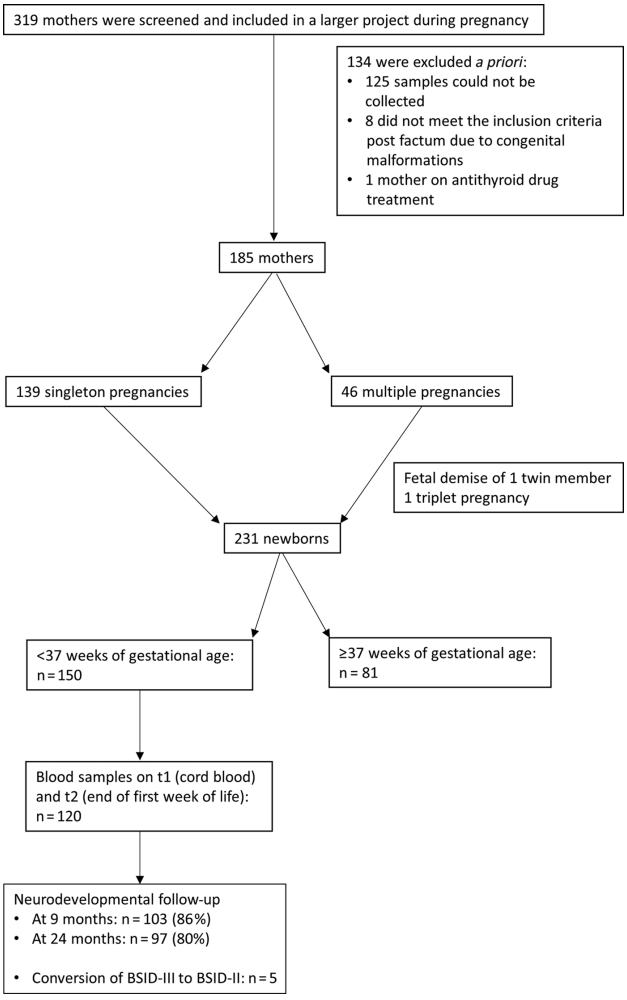

Figure 1: Patient selection flow chart.
n, number; BSID-II, Bayley Scales of Infant Development type 2; BSID-III, Bayley Scales of Infant Development type 3.

Impact of perinatal factors on the evolution of thyroid function during the first week of life

ΔT4

The perinatal events explained 30% of the variance in ΔT4 ($p \leq 0.0001$). Postnatal factors explained an additional 9% ($p = 0.02$). Both GA ($p = 0.001$) as well as the mode of delivery ($p = 0.04$) were significantly associated with ΔT4 (Table 2). Further analysis showed that 75% of the extremely low-GA neonates (GA <28 weeks, ELGANs) had decreased T4 levels at t2, whereas this was 25.5% in the infants with GA ≥28 weeks (Figure 2). Cord blood T4 levels were significantly higher in case of vaginal delivery compared to caesarean sections ($p = 0.03$), but comparable at t2 ($p = 0.3$). This resulted in statistically smaller differences in ΔT4 in vaginal deliveries with more negative trends, whereas in caesarean sections, there was an increasing evolution in T4 levels, resulting in larger and more positive differences in ΔT4 (data not shown). Dopamine use was the only postnatal factor significantly associated with lower ΔT4 ($p = 0.02$) (Table 2).

ΔfT4

The perinatal events accounted for 20% of the variance of ΔfT4 ($p = 0.001$). Postnatal factors explained an additional 8% ($p = 0.07$). Only GA ($p = 0.005$) was significantly associated with ΔfT4 (Table 2). Further analysis showed that 76.5% of the ELGANs had decreased fT4 levels at t2, whereas this was 25.5% in the infants with GA ≥28 weeks (Figure 2). Dopamine use before and/or at t2 was significantly associated with ΔfT4 ($p = 0.03$) (Table 2).

ΔT3

Perinatal events were responsible for 30% of the variance of ΔT3 ($p \leq 0.0001$). Postnatal factors explained an additional 5% ($p = 0.2$). Only GA ($p \leq 0.0001$) was significantly associated with ΔT3 (Table 2). Further analysis showed that 23.5% of the ELGANs had decreased T3 levels at t2, whereas this was 3.2% in the infants with GA ≥28 weeks (Figure 2).

There was a strong correlation between both ΔfT4 and ΔT3 (both $r = 0.6$; $p \leq 0.0001$). The lowest ΔfT4 levels accorded to negative ΔT3 levels.

TBG

ΔTBG was only available in 74 patients. There was a linear evolution in the function of GA (data not shown).

Impact of THOP on neurodevelopment

Table 3 gives an overview of patient characteristics of the infants of the follow-up study in relation to the predefined confounders, and Table 4 provides an overview of the

Table 1: Patient characteristics.

Maternal characteristics (n = 91)	
Mean age, years (±SD)	30.6 (±5.2)
Median BMI (n = 89) (±IQR)	23.5 (±5.5)
Smoking (n, %)	6 (6.6)
Higher education (n = 86) (n, %)	63 (73.3)
Assisted conception (n, %)	19 (21.6)
Thyroid disease (n, %)	5 (5.5)
Complete course of betamethasone (n, %)	77 (84.6)
Median GA (±IQR)	31.0 (±4.0)
Vaginal delivery (n, %)	24 (26.4)
Singleton vs. multiple pregnancy, %	57/34 (62.6/37.4)
Neonatal characteristics (n = 120)	
Sex (M/F), %	70/50 (58.3/41.7)
Median Apgar score at 1 min (±IQR)	8 (±2)
Median Apgar score at 5 min (±IQR)	9 (±1)
Median arterial cord blood pH (n = 109) (±IQR)	7.31 (±0.07)
Mean birth weight, g (±SD)	1577 (±556)
Median CRIB score (n = 64) (±IQR)	3.5 (±7)
Neonatal mortality (n, %)	2 (1.7)
Invasive ventilation at t2 (n, %)	14 (11.7)
Use of dopamine before and/or at t2 (n, %)	9 (7.5)
Use of hydrocortisone before and/or at t2 (n, %)	4 (3.3)
PDA at t2 (n, %)	11 (9.2)
Sepsis at t2 (n, %)	5 (4.2)
Treatment with levothyroxine after t2 (n, %)	12 (10)
Treatment with levothyroxine after t2 in the ELGAN population (n = 17) (n, %)	8 (47.1)
Breastfeeding (n, %)	107 (89.2)

BMI, body mass index; CRIB score, Clinical Risk Index for Babies, severity of illness score in infants with GA <31 weeks and/or birth weight ≤1500 g; ELGAN, extremely low for GA newborn (GA <28 weeks); F, female; GA, gestational age; IQR, interquartile range; M, male; PDA, patent ductus arteriosus; SD, standard deviation; sepsis, positive blood culture; t2, time 2, the moment of the second blood sample.

association of the predefined confounders with ΔT4, ΔfT4 and ΔT3 as well as the dichotomized and longitudinal BSID-II (the latter analysis was based on a model accounting for clustered data). GA, cranial ultrasound abnormalities and ROP were included in all the multivariable models. BPD was not associated with a BSID-II mental score <85 and therefore not included in that specific predicting model. Levothyroxine treatment was only associated with a BSID-II motor score ≤70 and only included in that predicting model.

Table 5 summarizes the results of the impact of the several Δs on the BSID-II scores. There was a trend toward a lower risk for a mental BSID-II score <85 with increasing ΔT3 at 9 months (p = 0.05), but not at 24 months (p = 0.6). The mental BSID score ≤75 and the BSID motor scores at 9 and 24 months were not affected by ΔT4, ΔfT4 or ΔT3.

Discussion

We described the natural evolution of TH levels in preterm infants during the first days of life. A decrease was influenced by low GA and *post hoc* analysis showed that mainly the ELGANs were vulnerable for this trend. The prohormone fT4 was more prone to decrease than T3 and the more ΔfT4 levels decreased, the more ΔT3 levels decreased, indicating the possible presence of maximal deiodination to the active T3, despite low availability of fT4. Unfortunately, reverse T3 levels were not available. Therefore, we could not obtain any information about the rate of possible T4 to reverse T3 inactivation, as known in the biochemically comparable non-thyroid illness syndrome [7].

Dopamine use was the only postnatal factor negatively associated with ΔfT4. Dopamine is known to suppress the TH function in preterm infants [8]. Besides positive inotropic and vasopressor effects through the stimulation of both α- and β-adrenoreceptors [9], it also acts on specific dopamine type 2 receptors in the anterior pituitary, leading to the inhibition of the release of prolactin, growth hormone and TSH [8].

A negative evolution in circulating T3 levels during the first week of life affects the infants' neurodevelopment in at least a temporary way. In the human fetus, cerebral T3 availability is mainly generated by local

Table 2: Hierarchical multivariable linear regression analyses determining significant and independent associations between first perinatal clinically relevant variables and second after addition of clinically relevant variables in the first week of life, and ΔT4, ΔfT4 and ΔT3.

Model	Variables	Estimated difference (95% CI) in plasma ΔTH levels	p-Value
ΔT4 (µg/dL)			
Perinatal variables ($R^2 = 0.3$, $p < 0.0001$)			
	GA (per week added)	0.4 (0.2 to 0.6)	0.001
	Mode of delivery (vaginal delivery vs. caesarean section)	1.1 (0.07 to 2.2)	0.04
	Prenatal administration of betamethasone (not given vs. given)	0.1 (−1.2 to 1.5)	0.9
	IUGR (not present vs. present)	−0.4 (−1.8 to 0.9)	0.5
	CRIB score (per unit added)	0.03 (−1.4 to 0.2)	0.7
	Maternal BMI (per unit added)	0.07 (−0.04 to 0.2)	0.2
	Maternal smoking state (not present vs. present)	0.2 (−1.7 to 2.0)	0.9
+ Postnatal variables ($\Delta R^2 = 0.09$, $p = 0.02$)			
	GA (per week added)	0.3 (0.07 to 0.6)	0.01
	Mode of delivery (vaginal delivery vs. caesarean section)	1.2 (0.09 to 2.2)	0.04
	Prenatal administration of betamethasone (not given vs. given)	0.2 (−1.1 to 1.5)	0.8
	IUGR (not present vs. present)	−0.2 (−1.6 to 1.2)	0.8
	CRIB score (per unit added)	0.09 (−0.1 to 0.3)	0 · 4
	Maternal BMI (per unit added)	0.06 (−0.05 to 0.2)	0.3
	Maternal smoking state (not present vs. present)	−0.6 (−2.5 to 1.2)	0.5
	Invasive ventilation at t2 (not present vs. present)	0.6 (−1.6 to 2.9)	0.6
	Dopamine use before and/or at t2 (not present vs. present)	−2.8 (−5.1 to −0.4)	0.02
	Hydrocortisone use before and/or at t2 (not present vs. present)	−0.2 (−2.9 to 2.4)	0.9
	PDA at t2 (not present vs. present)	−1.4 (−3.3 to 0.5)	0.1
	Sepsis at t2 (not present vs. present)	−0.9 (−3.2 to 1.4)	0.4
ΔfT4 (ng/dL)			
Perinatal variables ($R^2 = 0.2$, $p = 0.001$)			
	GA (per week added)	0.05 (0.02 to 0.09)	0.005
	Mode of delivery (vaginal delivery vs. caesarean section)	0.06 (−0.1 to 0.2)	0.5
	Prenatal administration of betamethasone (not given vs. given)	0.005 (−0.2 to 0.2)	0.9
	IUGR (not present vs. present)	0.02 (−0.2 to 0.2)	0.8
	CRIB score (per unit added)	0.00 (−0.03 to 0.03)	1.0
	Maternal BMI (per unit added)	0.01 (−0.004 to 0.03)	0.1
	Maternal smoking state (not present vs. present)	0.02 (−0.3 to 0.3)	0.9
+ Postnatal variables ($\Delta R^2 = 0.08$, $p = 0.07$)			
	GA (per week added)	0.04 (0.006 to 0.08)	0.02
	Mode of delivery (vaginal delivery vs. caesarean section)	0.07 (−0.09 to 0.2)	0.4
	Prenatal administration of betamethasone (not given vs. given)	0.02 (−0.2 to 0.2)	0.8
	IUGR (not present vs. present)	0.06 (−0.1 to 0.3)	0.5
	CRIB score (per unit added)	0.01 (−0.02 to 0.04)	0.4
	Maternal BMI (per unit added)	0.01 (−0.01 to 0.03)	0.2
	Maternal smoking state (not present vs. present)	−0.9 (−0.4 to 0.2)	0.5
	Invasive ventilation at t2 (not present vs. present)	0.03 (−0.3 to 0.4)	0.9
	Dopamine use before and/or at t2 (not present vs. present)	−0.4 (−0.7 to −0.05)	0.03
	Hydrocortisone use before and/or at t2 (not present vs. present)	−0.01 (−0.4 to 0.4)	0.9
	PDA at t2 (not present vs. present)	−0.1 (−0.4 to 0.2)	0.4
	Sepsis at t2 (not present vs. present)	−0.1 (−0.4 to 0.2)	0.6
ΔT3 (ng/dL)			
Perinatal variables ($R^2 = 0.3$, $p \leq 0.0001$)			
	GA (per week added)	5.6 (2.7 to 8.6)	0.000
	Mode of delivery (vaginal delivery vs. caesarean section)	−0.4 (−13.8 to 12.9)	1.0
	Prenatal administration of betamethasone (not given vs. given)	9.8 (−6.9 to 26.3)	0.2
	IUGR (not present vs. present)	−14.4 (−31.4 to 2.6)	0.1
	CRIB score (per unit added)	−0.7 (−2.9 to 1.5)	0.5
	Maternal BMI (per unit added)	0.6 (−0.8 to 2.0)	0.4
	Maternal smoking state (not present vs. present)	7.8 (−15.6 to 31.1)	0.5
+ Postnatal variables ($\Delta R^2 = 0.05$, $p = 0.2$)			
	GA (per week added)	5.0 (1.6 to 8.3)	0.004

Table 2 (continued)

Model	Variables	Estimated difference (95% CI) in plasma ΔTH levels	p-Value
	Mode of delivery (vaginal delivery vs. caesarean section)	−0.2 (−14.1 to 13.7)	1.0
	Prenatal administration of betamethasone (not given vs. given)	9.1 (−7.6 to 25.8)	0.3
	IUGR (not present vs. present)	−15.9 (−33.5 to 1.7)	0.08
	CRIB score (per unit added)	−0.5 (−3.1 to 2.2)	0.7
	Maternal BMI (per unit added)	0.5 (−0.9 to 1.9)	0.5
	Maternal smoking state (not present vs. present)	3.1 (−21.1 to 27.2)	0.8
	Invasive ventilation at t2 (not present vs. present)	14.3 (−14.8 to 43.5)	0.3
	Dopamine use before and/or at t2 (not present vs. present)	−16.0 (−45.8 to 13.8)	0.3
	Hydrocortisone use before and/or at t2 (not present vs. present)	−20.0 (−54.3 to 14.3)	0.3
	PDA at t2 (not present vs. present)	−19.8 (−44.1 to 4.4)	0.1
	Sepsis at t2 (not present vs. present)	4.0 (−25.1 to 33.0)	0.8

ΔTH levels, circulating thyroid hormone levels at time 2 (=during the first week of life)–thyroid hormone levels in cord blood (=time 1); BMI, body mass index; CI, confidence interval; CRIB score, Clinical Risk Index for Babies, severity of illness score in infants with GA <31 weeks and/or birth weight ≤1500 g; fT4, free thyroxine; GA, gestational age; IUGR, intrauterine growth restriction; PDA, patent ductus arteriosus; t2, time 2, during the first week of life; T3, triiodothyronine; T4, thyroxine.

deiodination of T4 [10]. Although the majority of ELGANs had a negative ΔfT4 balance, a negative ΔT3 balance was less frequent. We hypothesize that despite a low supply of T4, maximum conversion to the active hormone T3 is present in the brain, as adaptive mechanisms in brain deiodinase type 2 and deiodinase type 3 activity can help supply sufficient fT4 and T3 to brain cells in case of scarcity [11]. These adaptive mechanisms might not be fully developed in ELGANs [12]. This makes them most vulnerable to long-term sequels of THOP. It remains debatable whether this effect is temporary or permanent. The impact of a negative ΔT3 on the infants' neurodevelopment at the corrected age of 9 months was no longer present at the corrected age of 24 months, possibly due to the relative small sample size, patient drop-outs in the follow-up study, and the dynamics of brain development and neuroplasticity [13]. Moreover, the negative impact of low ΔT3 was only present in the infants with a mental BSID-II score <85, but not in the subgroup with a mental BSID-II score ≤70. This is probably also explained by the small sample size: nine patients had a BSID-II mental score <85 at 9 months, of whom four patients had a BSID-II mental score ≤70. These low patient numbers might have precluded a statistically significant association. Measuring BSID also remains a general way of establishing neurodevelopment. Further research should focus on other functions such as behavior and social interaction, and testing should also be performed at school age and beyond. Loss of patients in the follow-up study, both at 9 and 24 months, is a limitation of the study. A complicated pregnancy is often perceived as a traumatic experience and different coping mechanisms have been described [14]. Certain parents wish to leave this difficult period behind them and are not keen to participate in further follow-up programs.

A smaller ΔT4 was associated with vaginal delivery. *Post hoc* analysis showed that cord blood T4 levels were significantly higher in case of vaginal delivery. We could speculate that in case of vaginal delivery, labor already induces the TH surge more profoundly *in utero* [2, 15], resulting in increased cord blood T4 levels.

Both T4 and fT4 measurements are complex in preterm infants. When measured using commercial kits, as we did, fT4 measurements are an underestimation in case of low TH protein-binding capacity. The expensive and labor-intensive equilibrium dialysis is the gold standard for fT4 measurement, but rarely used in the clinical setting. With this technique, depression of T4 levels and maintenance of fT4 levels at 2 weeks of age in ELGANs were described [4]. Besides, heterogeneity in blood sampling at t2 is also a study limitation, as heparin was only administered in patients with an arterial line. Heparin releases plasma lipases, leading to increased plasma free fatty acids. They compete with T4 for binding to plasma binding proteins, causing an increase in fT4 levels [16]. Therefore, trends of both hormones were studied and were comparable.

One of the limitations of this study is that only trends in TH evolution in the first week of life were studied and not beyond. Adding more measurement points in time would have given us more information about the natural trends in TH evolution over a longer time span. Due to blood sample limitations in preterm infants, we focused on the evolution during the first week of life.

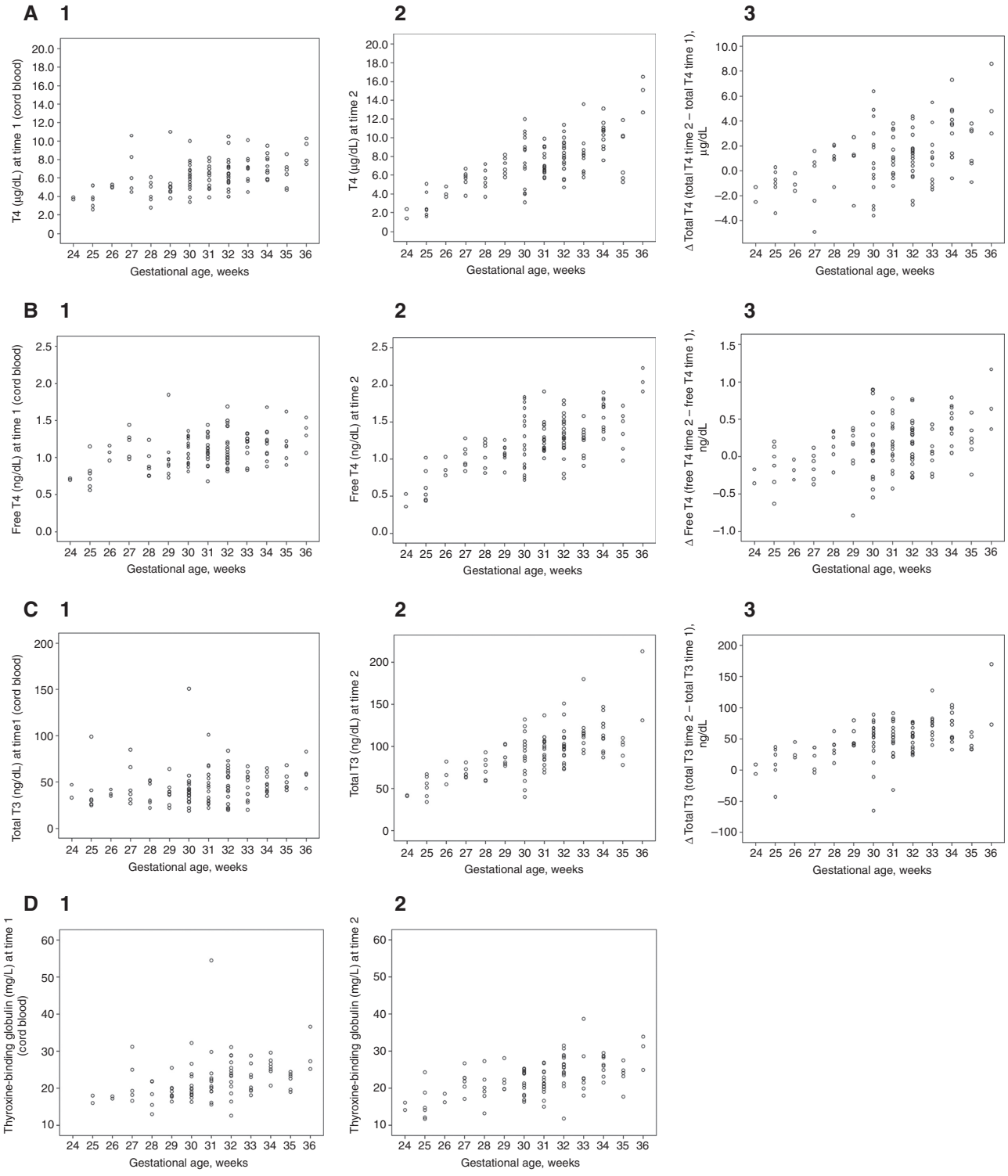

Figure 2: Evolution of circulating thyroid hormone levels at birth (cord blood), during the first week of life and net balance during the first week of life in the function of gestational age.
Panel A: Evolution of circulating thyroxine (T4) in the function of gestational age [1] in cord blood (t1); [2] during the first week of life (t2); [3] net balance during the first week of life: $\Delta T4 = T4$ at t2 – T4 at t1. Panel B: Evolution of circulating free thyroxine (fT4) in the function of gestational age: [1] in cord blood (t1); [2] during the first week of life (t2); [3] net balance during the first week of life: $\Delta fT4 = fT4$ at t2 – fT4 at t1. Panel C: Evolution of circulating triiodothyronine (T3) in the function of gestational age: [1] in cord blood (t1); [2] during the first week of life (t2); [3] net balance during the first week of life: $\Delta T3 = T3$ at t2 – T3 at t1. Panel D: Evolution of circulating thyroxin-binding globulin (TBG) in the function of gestational age: [1] in cord blood (t1); [2] during the first week of life (t2).

Table 3: Patient characteristics of the follow-up study in relation to the predefined confounding factors.

	Neurodevelopmental follow-up at 9 months corrected age (n = 103)	Neurodevelopmental follow-up at 24 months corrected age (n = 97)
Median GA, weeks (range)	31 (24–36)	31 (24–36)
Treatment with levothyroxine (n, %)	9 (8.7)	11 (11.3)
Abnormal intracranial ultrasound (n, %)	7 (6.8)	9 (9.3)
BPD (n, %)	10 (9.7)	11 (11.3)
ROP (n, %)	7 (6.8)	9 (9.3)
Sepsis (n, %)	17 (16.5)	17 (17.5)

Treatment with levothyroxine: levothyroxine 10 μg/kg for 14 days was initiated when free thyroxine levels were below 0.8 ng/dL at the end of the first week of life, according to the treatment regimen of the unit; abnormal intracranial ultrasound, grade II–IV intraventricular hemorrhage (IVH), persistent flaring >2 weeks and cerebral infarcts. BPD, bronchopulmonary dysplasia, defined as O2 and/or ventilation need at 36 weeks postmenstrual age; GA, gestational age; ROP, retinopathy of prematurity with need for laser therapy; sepsis, positive blood culture.

Table 4: Association of predefined confounders with dichotomized BSID-II, ΔT4, ΔfT4 and ΔT3.

Association with predefined confounders (p-values)							
Variable	**BSID-II mental score <85**	**BSID-II mental score ≤70**	**BSID-II motor score <85**	**BSID-II motor score ≤70**	**ΔT4**	**ΔfT4**	**ΔT3**
GA	0.008	0.0003	0.1	0.005	<0.0001	<0.0001	<0.0001
Levothyroxine treatment after t2	0.3	0.3	0.4	0.08	<0.0001	<0.0001	0.002
Cranial ultrasound abnormalities	0.04	0.007	0.05	0.0009	0.002	0.02	0.03
BPD	0.3	0.08	0.07	0.0008	0.001	0.003	<0.0001
ROP	0.04	0.0005	0.0002	<0.0001	0.01	0.01	0.02
Sepsis	0.8	0.5	0.8	0.3	0.03	0.02	<0.0001

Δ, delta (thyroid hormone levels at time 2 – thyroid hormone levels at time 1); BPD, bronchopulmonary dysplasia; BSID-II, Bayley Scales of Infant Development type II; fT4, free thyroxine; GA, gestational age; ROP, retinopathy of prematurity; t1, time 1 (cord blood); t2, time 2 (during the first week of life); T3, triiodothyronine; T4, thyroxine.

Although TH supplementation was initiated in some of our patients after t2, this variable was only associated with a BSID-II motor score ≤70 and, therefore, it was only included in that predicting model. Currently, there are no treatment guidelines for THOP [17], but the clinical reality with use of, for instance, pituitary-suppressing drugs sometimes requires a therapeutic approach. Nevertheless, further studies are needed. Prophylactic supplementation does not seem beneficial [18–20]. However, van Wassenaer et al. demonstrated a beneficial effect on the neurodevelopmental outcome of treatment in preterm infants with GA <28 weeks, which was still present at the age of 10 years. The reverse was true for those who were born at 29 weeks of gestation [21]. In the Thyroxine In Preterm Infants Trial (TIPIT), a double blind randomized placebo-controlled trial in ELGANs in the first 5 days of life, no difference in the width of subarachnoid space, measured at 36 weeks of corrected GA, between T4 supplementation and placebo could be demonstrated [19]. However, there was a significant correlation between low fT4 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 organized brain microstructure were associated with low plasma fT4 levels after birth [22]. Based on these and our current findings, we hypothesize that only infants with decreasing TH levels during the first week of life benefit from treatment. These patients should be the focus of further research. Besides, it remains questionable as to how long a negative balance can be tolerated, as a temporary interruption in TH supply in a critical time window may lead to irreversible brain damage [23].

Table 5: Impact of the evolution of thyroid hormones during the first week of life on BSID-II scores.

Variable	p-value interaction	Overall	
		OR (95% CI)	p-Value
Risk of moderate and severe abnormal BSID-II mental score (BSID-II mental score <85)			
ΔT4	0.3	0.92 (0.72–1.17)	0.5
ΔfT4	0.6	1.48 (0.27–8.17)	0.7
ΔT3	0.02	9 months	
		OR (95% CI)	p-Value
		0.97 (0.95–1.00)	0.05
		24 months	
		OR (95% CI)	p-Value
		1.01 (0.99–1.02)	0.6
Risk of severe abnormal BSID-II mental score (BSID-II mental score ≤70)			
ΔT4	0.6	0.83 (0.61–1.13)	0.2
ΔfT4	0.8	0.45 (0.05–3.73)	0.5
ΔT3	0.8	0.99 (0.97–1.01)	0.2
Risk of moderate and severe abnormal BSID-II motor score (BSID-II motor score <85)			
ΔT4	0.7	0.97 (0.80–1.18)	0.8
ΔfT4	0.9	1.04 (0.30–3.64)	0.9
ΔT3	0.9	1.00 (0.98–1.02)	1.0
Risk of severe abnormal BSID-II motor score (BSID-II motor score ≤70)			
ΔT4	0.2	0.90 (0.54–1.48)	0.7
ΔfT4	0.4	4.50 (0.06–351.16)	0.5
ΔT3	0.8	1.03 (0.99–1.08)	0.1

Δ, delta (thyroid hormone levels at time 2 – thyroid hormone levels at time 1); BSID-II, Bayley Scales of Infant Development type II; CI, confidential interval; fT4, free thyroxine; OR, odds ratio; t1, time 1 (cord blood); t2, time 2 (during the first week of life); T3, triiodothyronine; T4, thyroxine. OR > (<) 1, higher (lower) risk of abnormal BSID-II score with increasing Δ.

Also the ideal treatment regimen is uncertain. Excessive TH exposure might also affect brain development, and different treatment regimens have been used in several trials [24] [18, 19]. Finally, the hypothalamic-pituitary-thyroid axis immaturity might suggest a therapeutic role for thyrotropin-releasing hormone. Dynamic testing of the thyroid system by the administration of thyrotropin-releasing hormone in preterm infants has demonstrated a normal TSH response [25], but further studies are required.

In conclusion, a decrease in circulating TH levels during the first week of life is mainly an immaturity phenomenon, present in the majority of ELGANs. Dopamine further suppresses the hypothalamic-pituitary-thyroid axis. There is at least a temporary effect on the infants' neurodevelopment. Further trials should focus on those ELGANs with decreasing TH levels during the first week of life.

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