Clinical Study | E Cuestas and others | Risks of transient neonatal hyperthyrotropinemia | 172:4 | 1–9

Transient neonatal hyperthyrotropinemia is a risk factor for developing persistent hyperthyrotropinemia in childhood with repercussion on developmental status

Q1 **Eduardo Cuestas**[1,3,5], **María Isabel Gaido**[2,4] and **Raúl Horacio Capra**[2,4]

[1]Department of Pediatrics and Neonatology and [2]Clinical Biochemistry Department, Hospital Privado (IUCBC), Q2 Avenida Naciones Unidas 346, 5016 Cordoba, Argentina, [3]Faculty of Medical Sciences and [4]Faculty of Chemical Sciences, National University of Cordoba, Cordoba, Argentina and [5]Health Sciences Research Institute (INICSA), National Council of Scientific and Technical Research (CONICET), Cordoba, Argentina

Correspondence should be addressed to E Cuestas
Email
ecuestas@hospitalprivadosa.com.ar

Abstract

Objective: Transient neonatal hyperthyrotropinemia (TNH) is defined as a neonatal abnormality of thyroid function, which reverts to normal at re-examination after 2 weeks of life. The thyroid function of these infants has not been sufficiently studied in terms of the risk of developing persistent hyperthyrotropinemia (PH) in later childhood and its impact on growth and development.

Q3 *Design*: A prospective cohort study included all babies born in our Hospital between 2001 and 2006 and screened for Q3 hypothyroidism, whose thyroid function was re-examined 6 years later. Exclusion criteria included the following conditions: preterm birth, birth weight <2500 g, Down's syndrome, descendants of mothers with immune thyroid disease, congenital malformations, cardiac, renal, hepatic, and metabolic diseases, and steroid or dopamine medication. The variables included are TSH and thyroxine at neonatal screening and 6 years later. Main outcomes are the risk of developing PH in childhood, linear growth, and development using Parents' Evaluation of Developmental Status (PEDS).

Results: Out of 5040 normal-term newborns, 301 (6.0%, 95% CI 5.3–6.6%) have TSH ≥ 10 mU/l (TNH). Six years later, we re-examined 65 randomly selected children with TNH and 185 controls. In the TNH cohort, we found six out of 65 children (9.2%, 95% CI 1.4–17.0%) with PH (TSH ≥ 6.4 mU/l), and three out of 185 (1.6%, 95% CI 0.3–4.7%) among controls, relative Q3 risk 5.7 (95% CI 1.5–22.1), $P=0.0114$. TSH and developmental delay were found to be significantly higher in the TNH cohort (4.7 ± 1.3 mU/l vs 2.1 ± 0.5 mU/l, $P<0.0001$ and 15/65 (23%, 95% CI 12–34.1) vs 21/185 (11.3%, 95% CI 6.5–16.2) $P=0.0348$).

Conclusions: Newborns with TNH have a higher risk of developing PH in childhood, with repercussion on developmental status.

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Introduction

Q3 All newborns experience a state of thyroid-stimulating hormone (TSH) elevation after birth due to different stimuli, either exposure to cold in the ambient atmosphere or perinatal stress that may reach some very high levels during the first 36 h of life (1), and this physiological state should be well differentiated from transient neonatal hyperthyrotropinemia (TNH) defined as an abnormal transient elevation in neonatal TSH after 48 h of life, with normal thyroxine (T_4) values, which reverts to normality at re-examination after 2 weeks (2, 3). As a form of neonatal thyroid abnormality, it can result from temporarily active causes, which include prenatal iodine deficiency, prenatal iodine excess, maternal TSH_R-blocking antibodies, maternal antithyroid medication, mild gene mutations, isolated hyperthyrotropinemia (normal Q4 T_4, high TSH), maternal hypothyroidism, prematurity,

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very low birth weight, dopamine, steroids, hypothyroxinemia (low T_4, normal TSH), and hepatic hemangioma (3). Its incidence changes depending on how the condition is defined: whether it is based only on the confirmatory test or whether it is based on neonatal screening. In the latter, the expected incidence is higher. Confirmed congenital hypothyroidism (CH) occurs in one out of 3500–4000 live births, with a ratio of TNH/CH equal to 0.17/1, but the reported incidence indicates a broad variation between geographical areas and countries, due in part to disagreement in TNH/CH definitions (in Argentina, the incidence has changed from one out of 3108 with a 15 mU/l cutoff to one out of 2367 with a 10 mU/l cutoff) (4), analytical variability of screenings, population genetics, and ethnicity (5). TNH should be differentiated from false-positive screening test, defined as an abnormal screening test value, with normal results of serum tests taken immediately afterward. Obviously, these results should not be understood as an abnormal condition (6). TNH should be interpreted with caution in newborns, to assess the risk of unnecessary treatment, including: effects on brain development, hyperactivity, advancement in bone age, and craniosynostosis (7). There is considerable controversy regarding the long-term effects of TNH in the neonatal period on the development of persistent hyperthyrotropinemia (PH) during later childhood (age, 6 years), defined as a serum TSH level above the upper limit of the statistically defined reference range while the serum T_4 level is within the reference range, without clinical manifestations (8). Miki *et al.* (9) and Tyfield *et al.* (10) claim that TNH has no long-term adverse consequences, whereas Calaciura *et al.* (11) and Leonardi *et al.* (12) state that, in newborns with hyperthyrotropinemia (normal T_4 levels and elevated TSH levels on confirmatory test), this condition requires a considerable time frame to distinguish between permanent and transient cases, compared with normal controls having significantly higher TSH values in childhood; but unfortunately, these studies do not consider the question in appropriate epidemiological terms of the risk of developing PH in later childhood, and its potential impact on growth and development (13). In practice, our study addresses a question about the health of children who are diagnosed during neonatal screening programs with a mild transient form of thyroid dysfunction and for whom no clear evidence for treatment indications exists today.

For this reason, we test the hypothesis that TNH significantly increases the relative risk (RR) of developing PH at elementary school entry, and as secondary and tertiary objectives we compare linear growth and developmental status between the TNH and control cohorts.

Subjects and methods

Ethics statement

Written informed consent and the children's assent were obtained from all parents or guardians and patients (6 years old). The Hospital Privado Research Ethics Board authorized the study.

Design

This is an analytical, longitudinal, prospective cohort study, in which one group, called study cohort, comprised normal-term newborns with TNH (TSH $\geq$10 mU/l) and the other named control cohort comprised normal-term newborns without TNH (TSH $<$10 mU/l). Both groups were followed up until elementary school entry (6 years old), at which time they were re-examined.

Participants

Our subjects included all babies born between 01/01/2001 and 31/12/2006 in a general pediatrics university teaching hospital (Hospital Privado) setting screened for hypothyroidism (TSH at 2–3 days of life).

A second examination was carried out when TSH was $\geq$10 mU/l at $\sim$2 weeks of life (TSH $<$10 mU/l and T_4 8–18 pmol/l within a normal range) and, if both values were normal, the infant was considered to have TNH. Thyroid function was re-examined (TSH and T_4 within a normal range 0.8–6.4 mU/l and 6.9–16.2 pmol/l) 6 years later in both groups. Infants who were descendants of mothers with immune thyroid disease, those with low birth weight, Down's syndrome, congenital malformations, thyroid enlargement (Neonatal Goiter), confirmed hypothyroidism, and cardiac, hepatic, renal, and metabolic diseases, and those who were under steroid or dopamine medication were excluded.

Thyroid function evaluation

TSH and T_4 were measured in serum in all determinations by acquirable chemiluminescence (ECLIA) method (Roche diagnostics) using a Hitachi Modula E170 automatic analyzer, with an intra- and inter-assay coefficient of variation $<$3%. We did not use the whole blood drop placed on filter paper screening on account of its analytical

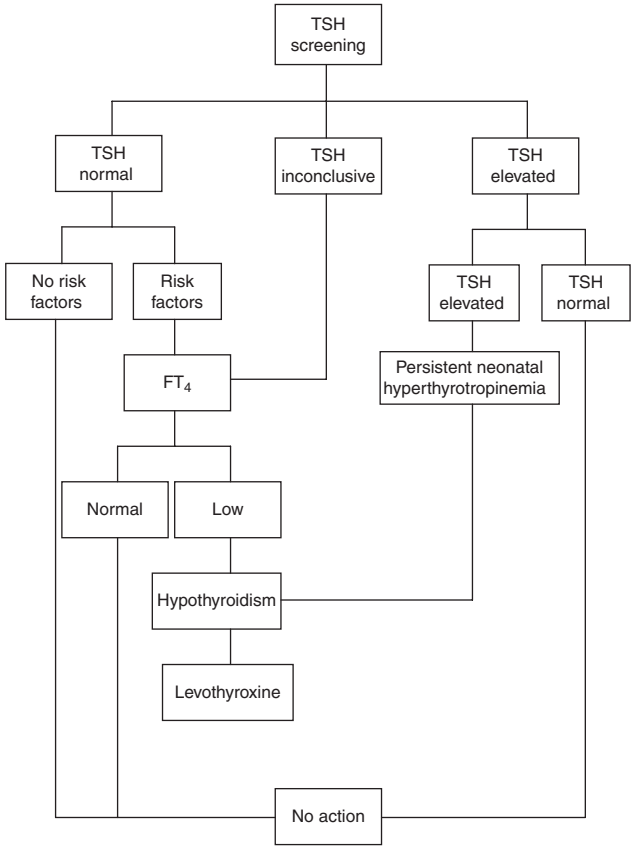

Figure 1
Flow diagram for screening congenital hypothyroidism.

inaccuracy since 2005. Figure 1 shows our guideline flow diagram for screening CH.

Clinical examination of subjects

All subjects underwent a complete physical examination by a trained and experienced pediatrician, who also recorded sex, height, and weight (*supine decubitus* in newborns and in standing position for 5–6-year-old children using a rigid standard stadiometer and a standard mechanical balance). Thyroid enlargement was determined by palpation (concordance >90% within observer E C), using masked prior ultrasound as gold standard during training (14, 15).

Auxological assessment

To enable comparison between different ages and sexes, heights were expressed as *Z*-scores and later transformed to sample mean age corresponding values, using WHO's international physical growth tables.

Developmental assessment

We assessed development by administering by telephone to parents a structured set of ten questions eliciting concerns in different areas of development (Spanish adaptation of Parents' Evaluation of Developmental Status (PEDS) questionnaire). This questionnaire is a rapid (<5 min) screening method, with very good sensitivity to suspected developmental delay. The test provides the general developmental and behavioral status in verbal, perceptual, motor, intellectual, behavioral, and relational domains. When the parents place two or more checks in the shaded boxes, the children meet criteria for special education services or perform below average in language, intelligence, and academics. Screening efficiency can be enhanced by a confirmatory test (16, 17).

Variables

The primary outcomes measured were TSH and T_4 values at neonatal recall and TSH and T_4 at elementary school entry. With these data, we considered TNH when TSH screening values were ≥10 mU/l, and returned to normal in almost 2 weeks (14 days of life) with normal T_4, and PH when TSH values were ≥6.4 mU/l at elementary school entry with normal T_4. The secondary outcome was to compare auxological parameters (height) and the tertiary outcome to compare general child development by PEDS. The final end point was the RR of developing PH at elementary school entry.

Data management

Biochemistry staff entered data in the Hospital Privado's electronic clinical record database developed by Hospital Privado's computer experts. Research staff collected the data directly from the computer system, verified all the data, and compared the database system and electronic clinical record results.

Sample size

Given that Calciura *et al*. found a prevalence of elevated TSH levels at re-examination in the TNH cohort of 36% and one of 8% in the control normal TSH cohort (10, 11), we estimated that 63 subjects for the TNH cohort and 189 for the normal control cohort (with a ratio of three controls per one exposed) were sufficient to test the hypothesis under study with $\alpha=0.05$ and $1-\beta>0.99$ and a confidence level of 0.95.

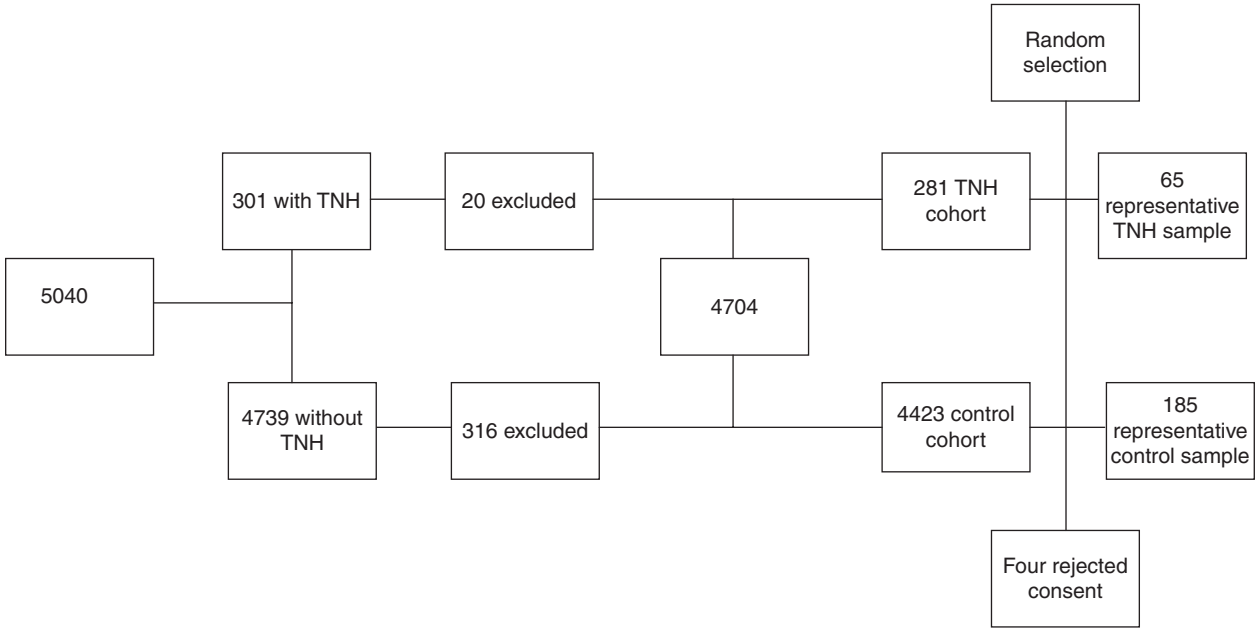

Figure 2

Representation of the procedure followed to recruit study subjects.

Random selection of subjects

All subjects in the database were divided into two blocks (children with TNH and children without TNH). In each block, we took a simple random sample using a computer-generated sequence; the process is described in Fig. 2. Researchers contacted the parents or caregivers by telephone and later recruited the participants and obtained the informed consent and assent. The statistician was masked (groups A and B) to data analysis.

Statistical analysis

Categorical variables are expressed as proportions with 95% CI, and continuous normally distributed variables as mean ± S.D. The statistical differences between both groups were assessed by the *t* test for continuous variables and the Fisher exact test for proportions. In a bivariate model, we calculated the RR with 95% CI. All statistical test results were considered to be significant if $P<0.05$. The analysis was performed using the EPIDAT software (version 3.1).

Results

We screened 5040 infants (2414 females, 47.9, 95% CI 46.5–49.3, and 2626 males, 52.1%, 95% CI 50.7–53.4) born at Hospital Privado between 01/01/2001 and 31/12/2006. Two infants had CH (2/5040 = 0.040%, 95% CI 0.005–0.143), one with thyroid agenesis and the other with dyshormogenesis. Out of 5040 infants, 301 (6.0%, 95% CI 5.3–6.6%) had TSH ≥10 mU/l (TNH), and, out of 301 infants, 193 were females and 108 were males (64%, 95% CI 58.4–69.6 vs 36%, 95% CI 30.3–41.6).

Out of 5040 infants, 201 were excluded for prematurity or birth weight <2500 g, nine for Down's syndrome, 25 for descendants of mothers with known immune thyroid disease, 35 for major congenital malformations, two for congenital permanent hypothyroidism, 57 for cardiac, hepatic, renal, or metabolic diseases, and three for steroid medication. A total of 4708 infants were in condition for random selection: 281 (6.0%, 95% CI 5.3–6.7) for the TNH cohort and 4423 (94.0%, 95% CI 93.3–94.7) for the control cohort. Four consents were withdrawn from the control cohort only. Two hundred and fifty clinically normal children remained after examination, random selection, and consent, 65 in the TNH cohort and 185 in the control cohort.

The basal conditions of the complete sample (250 subjects) were: at birth, mean age 2.2 ± 0.2 days, mean weight 3200 ± 250 g, mean height 50 ± 2 cm, mean head circumference 35 ± 2, 130 males (52%, 95% CI 45.6–58.4), 120 females (48%, 95% CI 41.6–54.4) and, at elementary school entry, mean age 5.5 ± 0.4 years, mean weight 20 ± 2.1 kg, and mean height 115 ± 4.8 cm.

Table 1 Results at elementary school entry.

Variables	Study cohort ($n=65$) $\mu\pm\sigma$ or % (95% CI)	Control cohort ($n=185$) $\mu\pm\sigma$ or % (95% CI)	*P*
Age	5.7±0.5	5.6±0.4	0.1485
Sex (female)	24/65 (36.9% (24.4–49.4))	96/185 (51.9% (44.4–59.4))	0.0437
Height	110.3±16.8	109.5±17.1	0.7448
Weight	19.6±1.7	19.3±1.5	0.2103
TSH (mIU/l)	4.7±1.3	2.1±0.5	<0.0001
T_4 (pmol/l)	15.1±1.9	14.9±2.1	0.4791
Suspected developmental delay (PEDS)	15 (23% (12–34.1))	21 (11.3% (6.5–16.2))	0.0348

There were no significant differences in initial characteristics between the TNH and control cohorts at birth, including age (2.1±0.4 vs 2.2±0.5 days, $P=0.1076$), weight (3280±251 g vs 3225±248 g, $P=0.1303$), height (50.1±2.1 vs 50.2±2, $P=0.7388$), and head circumference (35.3±2.1 vs 35.1±2, $P=0.4950$). With regard to sex distribution, 24 out of 65 (36.9%, 95% CI 24.4–49.4) were females against 96 out of 185 (51.9%, 95% CI 44.4–59.4) females, $P=0.0437$.

At elementary school entry, 6 years later, the comparison between the TNH and control cohorts showed no significant differences in age, weight, height, or T_4. PEDS development scores, TSH, and female sex distribution were significantly lower in the TNH cohort (Table 1).

Out of 65 subjects, six have PH (TSH ≥6.4 mU/l; 9.2%, 95% CI 1.4–17.0) and, out of 185 subjects, three have PH (TSH ≥6.4 mU/l; 1.6%, 95% CI 0.3–4.7). The RR of developing PH in TNH was 5.7, 95% CI 1.5–22.1, $P=0.0114$. Of the six subjects with TNH, four out of six were females (66.6%, 95% CI 22.2–95.6).

Discussion

In this relatively large, hospital population-based, random selection longitudinal cohort study, we tested the hypothesis that TNH significantly increases the RR of developing PH at elementary school entry. As the main result, we found a significant increase in RR of developing PH in later childhood in children with TNH, with no repercussion on linear growth but with a clinically important compromise in developmental status (PEDS).

The population in this study is similar to that reported in 2002 by Calaciura *et al.* (11), in 2008 by Leonardi *et al.* (12) and in 2013 by Oren *et al.* (18). Our work showed a lower prevalence of PH in children with TNH, 9.2% vs 50% in the first cited authors, 43.2% in the second, and 22.3% in the third. We explain these differences based on the following: our population was selected using a much stricter exclusion criterion; the study was randomly selected and population based; the method of obtaining TSH measurements varies between the studies; and different upper confidence limits were used to consider elevated TSH. However, the tendency is the same because the results are statistically significant in all studies, and our results confirm the results obtained by these authors. We found a significantly higher proportion of TNH in females in concordance with the findings of Medda *et al.* (19) at birth, a fact that remains constant at elementary school entry. It is still unclear as to why females are more susceptible to developing TNH, but it is more frequent in Hispanic females (3:1 or one in 1886 births) than the other ethnic groups except Afro-American newborns. Ethnic characteristic may play a role in this sex disparity, possibly because the preponderance in females is mostly associated with dysgenesis of the thyroid gland (20).

Our study also confirms the finding that mean TSH levels are higher in children with antecedents of TNH, indicating that thyroid function is not completely normal, but compensates with a normal T_4 secretion (21), and the fact that linear growth was similar in both cohorts, possibly due to a compensatory effect on growing large bone tissue for this reason (13, 14).

Calciura *et al.* and Leonardi *et al.* do not consider developmental status in their studies. The long-term clinical consequences of compensated hyperthyrotropinemia beginning in early life have not been sufficiently researched, and it is biologically plausible that isolated hyperthyrotropinemia causes minimal abnormalities, with very subtle manifestations. In pediatric populations, Ávarez-Pedrerol *et al.* (22) as well as Freire *et al.* (23) found an inverse association between TSH levels (within the normal range) at birth and later neurocognitive functions in childhood (higher TSH levels have lower scores in subsequent cognitive testing methods). In consonance with our results, Ávarez-Pedrerol *et al.* argued that TSH concentrations inversely reflect tri-iodothyronine (T_3) and T_4 sensed by the pituitary gland. Each individual has a genetically determined free T_4 set-point and any excess or deficiency will be sensed by the individual's pituitary and cause an inverse response in TSH secretion, hence serum TSH outside the population reference values indicates that serum T_3 and T_4 were abnormal for the individual. This point is highly significant because it makes it possible to postulate the biological plausibility that 'normal' levels of thyroid hormones can be physiologically inappropriate according to current knowledge, causing alterations in

neuropsychological function in childhood. The prevalence of TNH has increased in one Canadian study during the last decade from 10% in 2000 to 43% in 2010 (18). This fact probably reflects an adaptation of endocrine process to environmental modifications (possibly iodine uptake blockers) that induce epigenetic changes; Calebiro *et al.* (24) report a prevalence of 11.8% genetic alterations in TSH receptor with variable signaling impairment in children with non-autoimmune isolated hyperthyrotropinemia. Thus, in contemporary humans, a major function of TSH may be to conserve iodine for thyroid hormone synthesis during periods of scarcity. It should be pointed out in the context that adjustment of intermittent feeding results in epigenetic changes in certain genes, such as those causing obesity and type 2 diabetes mellitus, according to Barker's thrifty genotype hypothesis (25). Thus, not only relative levels of T_3 and T_4 but also high levels of TSH alone could induce alterations in neonatal brain development. The identification of TSH receptors in non-thyroid tissue, especially in the brain, has been reported in recent years. Interestingly, the gene expression of TSH receptors in the hippocampus and cortex was regulated throughout the neonatal period and correlated positively with the level of circulating TSH in serum (26), suggesting that TSH may regulate the expression of TSH receptors in the brain. The pattern of the expression suggests additional physiological roles. In the dentate gyrus, where the TSH receptor gene expression in neuronal cells culminated, neuronal precursors have been observed. Progenitor cells, which can ultimately differentiate into both neuronal and astroglial cells, are found in the CNS during development. Most precursors migrate toward their final location, and they fully differentiate. While astroglial cells are well known to keep a potential for proliferation in the adult brain, neurons were thought, until recently, to have lost this potential. Moreover, enhancement of the TSH receptor transcript level in the brain coincided with a dramatic rise in thyroid hormone β-receptor expression. The thyroid system is implicated in neuronal development within the neonatal period. It was therefore tempting to link the enhancement of the expression of TSH receptor to that of thyroid hormone β-receptor, perhaps in relationship with the commitment of neuronal precursor in the brain at birth (27). These facts would strongly support the hypothesis that elevated TSH levels during the neonatal period, even within the upper normal range, would be related to lower scores in childhood cognitive development.

The strengths of this study include its relatively large representative population base, random selection, which ensures the representativeness of the sample and the absence of statistical biases even with a relatively low number of children with TNH, because convenient cohorts can cause inclusion bias (the consistency of the results between the two cohorts in most of the outcomes reinforces their validity), simple design, and the use of clinically available, inexpensive, and reproducible methods. To our knowledge, this is the first report to evaluate the effect of TNH on developmental status in a large cohort study.

A debatable weakness is that we measure the cognitive outcome in terms of developmental status screening and not in terms of IQ confirmatory test, but PEDS has a very good tool for detecting developmental delays, especially when two or more questions are positive; it indicates a 20 times higher risk of having delays in language, intelligence, and academics. Furthermore, the same test was given independently to both cohorts equally, which were measured using the same instrument by the same professionals (17). PEDS is a screening questionnaire for suspected developmental disorders, designed for the primary care pediatrician as an alternative to informal milestone checklists. The test has been standardized and validated with a sensitivity of 83% and a specificity of 84% compared with The Brigance Inventory of Early Development-II (IED-II) and The Brigance Comprehensive Inventory of Basic Skill-Revised (CIBS-R) (28). PEDS has been used in research to assess development in children with neurofibromatosis and autism, among others (29, 30).

The question that needs to be answered is which of the reference intervals implied a specific new definition of what constituted a significant rise, and when and how to treat these children. This study recapitulated the intended real-world use of TSH screening utilized in the context of the individual child with a potential risk of growth and development delay, alterations in lipid metabolism and heart function, among others, and the subsequent development of overt hypothyroidism (31). For these reasons, we usually treat infants with PH with levothyroxine (L-T_4), at any age, as long as TSH levels remain above 10 mU/l in at least two determinations, separated by intervals of not <3 months, even with a normal ultrasound, normal ioduria, and absence of antithyroid antibodies. We are aware that this issue is controversial, but in the light of other authors' results and our own results, this approach seems to be accurate to us (23).

Unfortunately, we cannot study a recently described relationship between IVF and subclinical hypothyroidism or PH (32).

We conclude that TNH increases the RR of developing PH in later childhood, with no repercussion on linear growth but with clinically important consequences on language, intelligence, and academic developmental delays. Based on this evidence, we recommend that there is a need for re-evaluating normal TSH upper interval limits, and in the meantime, to treat the patients with TNH with appropriate doses of L-T_4 to maintain the mean levels of TSH with a close clinical and laboratory (TSH, T_4) monitoring, including the challenge of removing the medication after 2 years, to re-evaluate their need. These results should be confirmed in large multicenter follow-up studies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

E Cuestas was involved in study conception and design. E Cuestas, M I Gaido, and R H Capra contributed to acquisition of data. E Cuestas and R H Capra performed analysis and interpretation of data. M I Gaido drafted the manuscript. E Cuestas critically revised the final version of the manuscript.

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