Prediction of Neonatal Hyperthyroidism

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Objectives To assess whether it is possible to identify the neonatal predictors of neonatal hyperthyroidism at the presymptomatic stage of the disease.

Study design This retrospective multicenter study in 10 maternity units was based on the medical records of all patients monitored for a pregnancy between January 1, 2007, and January 1, 2014. Among 280 000 births, 2288 medical records of women with thyroid dysfunction were selected and screened. Of these, 415 women had Graves disease and were positive for thyrotropin receptor antibody during pregnancy, and were included.

Results A thyroid-stimulating hormone (TSH) level of less than 0.90 mIU/L between days 3 and 7 of life predicted neonatal hyperthyroidism with a sensitivity 78% (95% CI, 74%-82%) and a and specificity of 99% (95% CI, 98%-100%), a positive predictive value of 90% (95% CI, 87%-93%), a negative predictive value of 98% (95% CI, 97%-99%), and an area under the receiver operating characteristic curve of 0.99 (95% CI, 0.97-1.0). A thyrotropin receptor antibody (TRAb) elimination time was calculated using the equation: $7.28 + 2.88 \times \log() + 11.62 \log(\text{TRAb}^2)$.

Conclusions All newborns with a TSH level of less than 0.90 mIU/L should be examined by a pediatrician. Using TSH, it is possible to screen for neonatal hypothyroidism and for neonatal hyperthyroidism with a TSH cutoff of 0.90 mIU/L, and this shows the relevance of our study in terms of public health. *(J Pediatr 2018;197:249-54).*

Neonatal hyperthyroidism (NH) is mainly related to transplacental passage of maternal anti-thyrotropin receptor antibodies (TRAbs).[1] Other causes of NH are an activating mutation of the thyroid-stimulating hormone (TSH) receptor and activating mutation of the stimulatory G protein in McCune-Albright syndrome.[2] The incidence of NH is between 1% and 5% in all women with active or past Graves disease.[3] Untreated, rare and severe disease has a fetal and neonatal mortality rate of 25%.[4]

Thyroid hormones play an essential role in ensuring normal development of the fetus, particularly of the central nervous system. The deiodinases enzymatic system (D2, D3), responsible for the conversion of inactive forms of thyroid hormone and inversely according to the type, allows the fetal brain to optimize the local production of biologically active free triiodothyronine (FT3). D2 receptors in the brain appear after approximately 7 weeks of gestation. Their number and expressivity increase with the development of the fetal thyroid. This complex regulation in time and space of expressivity is defined by critical periods when thyroid hormones are necessary for the development of some parts of the central nervous system and for the myelination of nerve fibers, which is essential for normal motor skills. This process begins very early in development and continues after birth.[5,6]

Thyroid hormones are important regulators of cardiac gene expression; many of the cardiac manifestations of thyroid dysfunction are associated with alterations in FT3-mediated gene expression. The clinical manifestations of fetal and NH are dominated by effects of thyroid hormones on the heart and cardiovascular system. Excessive thyroid hormone production has contrasting effects on the cardiovascular system: hyperthyroidism decreases systemic vascular resistance, but increases cardiac output, heart rate, and intravascular blood volume.[7,8] Heart failure is one of the major risks of congenital hyperthyroidism in the neonate.

NH is mainly described and predicted as a continuity of the mother's Graves disease.[9-20] There are a few multicenter studies describing the predictors factors of NH. The aim of this study was to establish how to predict NH from neonatal variables during the presymptomatic stage of the disease.

AUC	Area under receiver operating characteristic curve
FT3	Free triiodothyronine
FT4	Free thyroxine
NH	Neonatal hyperthyroidism
PMSI	Programme de Médicalisation des Systèmes d'information
TRAbs	Thyrotropin receptor antibodies
TSH	Thyroid-stimulating hormone

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Methods

This retrospective multicenter study was based on data from the medical records of all patients monitored for a pregnancy between January 1, 2007, and January 1, 2014, in 10 obstetric centers of the Assistance Publique des Hôpitaux de Paris–AP-HP (Beaujon, Bichat, Robert Debré, Antoine Béclère, Kremlin-Bicêtre, Trousseau, Necker-Enfants-Malades, Louis Mourier, Port Royal, Pitié Salpêtrière). Women with Graves disease who were positive for TRAb at least once during pregnancy were included. The protocol was approved by the Paris Nord Evaluation and Research Committee of Biomedical Research Projects, (CEERB Paris Nord, authorization number no. 13-066), the Consulting Committee on Information Processing in Health Research (CCTIRS, authorization number no. 13.296), and the French Data Protection Authority (CNIL, authorization number no. 6IZ084649b).

A list of pregnant women with thyroid disease followed up in the study was provided by the medical information department of each hospital (Programme de Médicalisation des Systemes d'information [PMSI]). The PMSI database provides detailed medical information on all admissions to French hospitals, including discharge diagnosis using *International Classification of Diseases, 10th edition,* codes as follows: E05, E05.0, E05.4, E05.5, E05.8, E05.9, E06.0, E06.1, E06.2, E06.3, E06.9, P72.1 (www.who.int/classifivations/icd/en/). Then, we screened the medical records of these patients to select those presenting Graves disease who were positive for TRAb (>1 IU/L) at least once during pregnancy.

Clinical and Biochemical Data

NH was defined as the presence of ultrasound neonatal thyroid hypertrophy (goiter) or clinical signs of NH: heart rate of more than 160 bpm (tachycardia), heart failure, pulmonary arterial hypertension, hyperexcitability, poor weight gain despite appropriate daily intake, vomiting, diarrhea, and craniosynostosis.[21,22] We estimated that a neonatal thyroid hypertrophy on ultrasound examination (which is not well-standardized) without any other clinical or biochemical signs was not a clinically significant form of NH.

TRAb was measured in the peripheral blood in accordance with the serum sample method. TRAb was determined with a second-generation human assay with TRAb (Human Recombinant TSH receptor h-TBII assay; B.R.A.M.H.S. Diagnostica, Berlin, Germany). TRAb were detected when their concentration was greater than 1 IU/L. No discrepant results necessitated studies of TRAb activity.[23]

The TRAb elimination was defined as the value corresponding to a TRAb rate, which is lower than 1 UI/L in the child's blood. The equation TRAb elimination time was calculated based on data directly collected during medical follow along.

TSH was measured in the peripheral blood in accordance with the serum sample method and not with dried blood spots. The same method of hormonal measurement was performed between day 3 and day 7 by all the hospitals included in this study. A 2-mL blood sample was collected from all the newborns following the same method. Serum FT3, free thyroxine (FT4), and TSH concentrations were determined by immunochemiluminescent assays (Siemens Healthcare Diagnostics SAS, Saint-Denis, France). Analytical methods were controlled according to the manufacturer's instructions.

For the cesarean delivery, we assumed that the low transplacental crossing after the anesthesia procedures did not impact on the level of TSH for the newborns that were sampled 3 to 7 days after birth. Medications used during cesarean delivery anesthesia were bupivacaine, suxamethonium, sufentanil, morphine, xylocaine, thiopental, and sevoflurane. In 90% of cases, the cesarean delivery was made by epidural analgesia and in 10% of the cases, general anesthesia was used.

The 2.5th and 97.5th percentiles of thyroid hormone levels of newborns from days 1 and 30 of life were as follows: FT3, 1.8-10.4 pmol/L; FT4, 10.9-34.5 pmol/[24]; and TSH, 1.8-9.7 mIU/L.[25] Neonatal biochemical hyperthyroidism was defined, between days 3 and 7 of life, by a TSH level of less than the 2.5th percentile and an FT4 level of greater than the 97.5th percentile.[4]

Statistical Analyses

We performed the same assays in all centers; data collection was done within the same period of time and it was carried out by a single doctor in the 10 centers who, thus, automatically ensured the coherence of the database during the entry of the data. The data were then collected in each center and merged into a single database, including a quantity check on the final folder.

Categorical variables were compared using χ^2 tests and continuous variables using the Student t test (or the Wilcoxon test in the case of non-normality). Demographic and clinical characteristics were summarized at baseline as counts and percentages of the total numbers of patients, as mean ± SD for normally distributed continuous variables, and as median (IQR) for other continuous variables. $P < .05$ was considered significant. Because TRAb and thyroid hormones were not normally distributed, the data were natural log transformed for TRAb from days 0 to 5, FT4 from days 3 to 7, and TSH from days 3 to 7. Pairwise Pearson correlation coefficients were computed for those predictors. Using a multivariate logistic model, aORs (95% CI) were computed to measure the association between the development of NH and potential predictors or confounders. This regression model included only 3 variables (TRAb days 0-5, FT4 days 3-7, and TSH days 3-7) to account for the fact that there were a limited number of positive cases (n = 23; **Table I**). The variables included in the multivariate model were chosen on the basis of criteria of statistical significance and clinical relevance. A goodness-of-fit test for continuous variables (TSH levels from days 3 to 7, FT4 levels from days 3 to 7, TRAb levels from days 0 to 5) was assessed using the Hosmer-Lemeshow statistic. A receiver operating characteristic analysis was used to compute sensitivity, specificity, positive predictive value, and negative predictive value in predicting NH. The cutoff of TSH was chosen to predict NH by maximizing specificity to have as few false positives as possible among all the positive subjects. Linear regression was used to assess the relationship between elimination time

Table I. Risk factors for development of NH*

Predictor variables	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis aOR (95% CI)	*P* value
Log(FT4), days 3-7, pmol/L	17.58 (4.92-62.86)	<.0001	0.13 (0.01-1.67)	.12
Log(TSH), days 3-7, mU/L	0.23 (0.14-0.38)	<.0001	0.47 (0.28-0.80)	.005
Log(TRAb), day 0-5, IU/L	31.73 (6.67-150.96)	<.0001	26.70 (3.48-204.81)	.002
TSH cutoff (days 3-7) = 0.90 mU/L (N = 415)				
Sensitivity, % (95% CI)				78 (74-82)
Specificity, % (95% CI)				99 (99-100)
Positive predictive value, % (95% CI)				90 (87-93)
Negative predictive value, % (95% CI)				98 (97-99)
Correctly classified, %				98

*In the population of all women (N = 415), according to univariate and multivariate logistic regression model analyses showing the aOR.

and TRAb (in log units). A quadratic term was added to account for slight nonlinearity when TRAb increased beyond 3 log units (ie, 20 units). A fixed error rate of 5% was considered for all statistical analyses. All data were processed with STATA 13 software (StataCorp LP, College Station, Texas; http://www.stata.com).

Results

Among 280 000 births, 2288 medical records of women with thyroid dysfunction were selected and screened: 417 women had Graves disease and were positive for TRAb during pregnancy, 2 patients were excluded from the study (their newborns developed hypothyroidism) and 415 women were included.

Among 415 women, 143 patients had only 1 TRAb (1-50 mUI/L) determination between 10 and 38 weeks of gestation and 272 patients had more than 1 TRAb (1-480 mUI/L) determination between 5 and 38 weeks of gestation (167 had 2 determinations, 63 had 3, and 42 had >3). In 98.2% of the cases, the first value was the highest.

In these 415 pregnant women, 23 newborns (5.5%) presented NH, the mothers of 20 newborns (87%) were undergoing synthetic antithyroid drug treatment in the last trimester of gestation; only 3 mothers (13%) were free of antithyroid drug. Children with NH were born earlier (mean of 37 weeks of gestation vs 38.5 weeks of gestation; $P = .005$) and had a significantly lower birth weight (mean of 2809 g vs 3103 g; $P = .03$). Of the newborns, 83 (19.8%) were admitted to the neonatal intensive care unit, 29 (6.9%) had an FT4 level of greater than the 97.5th percentile, 23 (20%) had a TSH level of less than the 2.5th percentile, and 17 (4.1%) had biochemical hyperthyroidism (**Table II**). The clinical signs varied in severity: neonatal thyroid hypertrophy in 15 (65.2%), hyperexcitability in 7 (30.4%), increased appetite but poor weight gain in 7 (30.4%), vomiting in 5 (21.7%), pulmonary arterial hypertension documented by echocardiography in 1 (4.3%), and sinus tachycardia in 16 (69.6%), with heart failure in the 4 cases. Only 17 children received hormonal therapy by propylthiouracil (35.3%) or by carbimazole (64.7%). In 10 cases, we also used propranolol to control tachycardia during the first 10 days of treatment and for 14 newborns synthetic antithyroid drug therapy was followed by levothyroxine. There were 149 newborns (35.9%) with positive TRAb tests, with a median TRAb elimination of 20 days (IQR, 15-35 days). The estimated relationship between TRAb and its duration of elimination is given by the following equation:

$$\text{TRAb elimination time}(\text{day}) = 7.28 + 2.88 \times \log(\text{TRAb}) + 11.62 \log(\text{TRAb}^2)$$

The slope was significantly different from zero ($P = .007$ for log[TRAb] and $P = .002$ for log[TRAb^2]). This model accounted for 60.2% of the variance (**Figure 1**). The correlation coefficient was between log(TSH)/log(FT4) ($r = -0.32$; $P < .0001$) and log(TSH)/log(TRAb) ($r = -0.62$; $P < .0001$).

In the univariate model, a statistically significant association between log(FT4) levels (days 3-7) and NH became nonsignificant after adjustment (aOR, 0.13; 95% CI, 0.01-1.67; $P = .12$). Concerning log(TSH) levels (days 3-7), a negative association with NH remained statistically significant even after adjustment: the lower the TSH level, the higher the risk (aOR, 0.47; 95% CI, 0.28-0.80; $P = .005$; **Table I**). The multivariate regression analysis revealed that TRAb levels and TSH levels in the child were the strongest independent predictors of NH (**Table I**). Regarding goodness of fit, expected frequencies were not significantly different from observed frequencies according to the Hosmer-Lemeshow test ($P > .05$).

A TSH level of less than 0.90 mIU/L between days 3 and 7 of life predicted NH with a sensitivity of 78% (95% CI, 74%-82%) and a specificity of 99% (95% CI, 98%-100%), a positive predictive value of 90% (95% CI, 87%-93%), a negative predictive value of 98% (95% CI, 97%-99%), and an area under the curve of 0.99 (95% CI, 0.97-1.0; **Figure 2**).

Discussion

Despite regular data audits of the PMSI database,[26] our study is limited by its retrospective nature, and the participation of several centers, which make it less robust and more heterogeneous. Also, the study was conducted on the newborns of

Table II. Description of the population

Variables	NH Yes (n = 23)	NH No (n = 392)	Uncorrected *P* value
Nonlaboratory data			
Levothyroxine (mother)			.29§
Yes	8 (34.8)	167 (42.6)	
Antithyroid drugs (mother)			<.0001§
Yes	20 (87)	125 (31.9)	
Term (wk)	37.0 ± 1.9	38.5 ± 2.4	.005*
Vaginal delivery	13 (56.5)	247 (63.0)	.69‡
Instrumental delivery	3 (13.0)	45 (11.5)	
Cesarean section	7 (30.4)	100 (25.5)	
Sex			.89‡
Boy	12 (52.2)	202 (51.5)	
Birth weight (g)	2809.8 ± 631.5	3103.4 ± 650.2	.03*
Admission to NICU			<.0001‡
Yes	21 (91.3)	62 (15.8)	
Laboratory data			
TRAb IU/L (mother)	50.0 (17.3-102.0)	1.8 (1.3-4.4)	<.0001†
pH (cord blood)	n = 14	n = 272	.50*
	7.26 ± 0.8	7.28 ± 0.9	
FT3 from day 3 to 7 (pmol/L)	n = 18	n = 317	<.0001*
	10.2 ± 7.7	6.2 ± 1.9	
FT4 from day 3 to 7 (pmol/L)	37.0 (25.2- 50.0)	22.5 (19.3- 26.8)	<.0001†
TSH from days 3-7 (mU/L)	0.06 (0.01-0.9)	5.6 (2.7-7.8)	<.0001†
TSH <2.5th (1.8 mIU/L)			<.0001‡
Between days 3 and 7	23 (100)	60 (15.1)	
FT4 >97.5th (34.5 pmol/L) from day 3 to 7	12 (52.2)	17 (4.34)	<.0001‡
Biochemical hyperthyroidism from day 3 to 7			<.0001‡
Yes	12 (52.2)	5 (1.3)	
TSH ≤0.90 mU/L from day 3 to 7	18 (78.3)	5 (1.2)	<.0001‡
TRAb from day 0 to 5 (IU/L)	24.0 (11.3- 41.0)	0.9 (0.9-1.5)	<.0001†

NICU, Neonatal intensive care unit.
Data are n (%) relative to neonatal thyroid status, as mean ± SD for normally distributed continuous variables, as median (IQR) for other continuous variables.
*Student *t* test.
†Wilcoxon test.
‡χ^2 test.
§Fisher exact test.

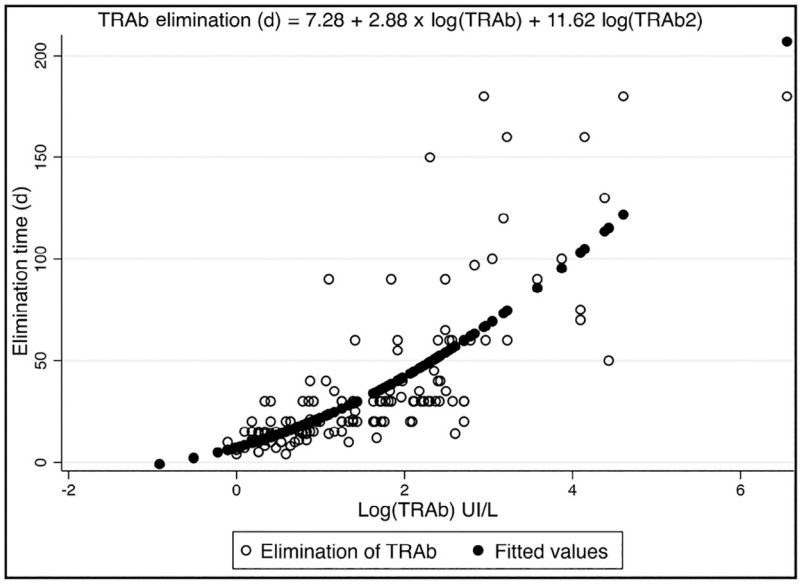

Figure 1. The estimated probability of TRAb elimination (days 0-5) based on the fitted model.

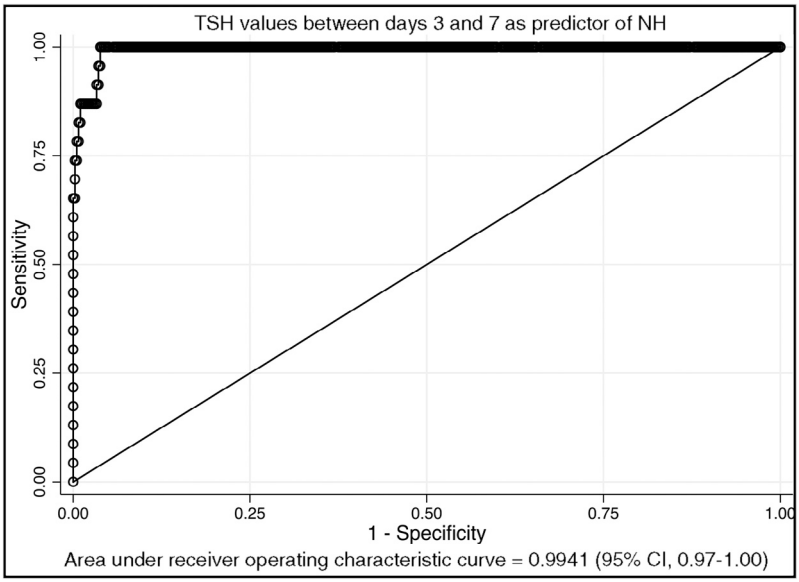

Figure 2. Association between newborn TSH values (days 3-7) and NH.

mothers with Graves disease, and this may be a source of bias. Despite these limitations, we have been able to draw interesting conclusions concerning the screening and management of NH.

Neonatal screening for congenital hypothyroidism was introduced in 1975.[27] Since its establishment, this program has precluded many cases of intellectual disability. In France, it is based on TSH determination on dried blood collected on filter paper at 3 days of life, but the dosage is not calibrated to identify newborns with low TSH levels. In congenital hyperthyroidism, craniosynostosis can lead to intellectual disability, but, apart from such cases, affected children show normal intellectual development. In general, the main complication of NH remains heart failure. NH usually is associated with maternal Graves disease and most cases are clinically suspected and managed during pregnancy[28]; however, when the mother has not been screened, diagnosis of the newborn can be delayed and the consequences of heart failure will be dramatic. It is for this reason that it is essential to identify affected children at the presymptomatic stage of the disease.

Our study shows that FT4 levels above the 97.5th percentile identified 52.2% of children with NH. When adjusted to TSH and TRAb levels, FT4 lost statistical significance as a predictor of NH. The correlation between FT4 and TSH cannot be the only possible explanation, because TSH is a more sensitive biomarker of NH than FT4.

Based on the fitted model, we estimated for each subject in the dataset the time of elimination of TRAb, which is useful information for the management of NH. We, therefore, know at birth how long the child will take to eliminate the maternal antibodies and can schedule pediatric follow-up accordingly. The equation for the TRAb elimination time will help clinicians to determine the length of the elimination of these antibodies at the moment of birth. Thus, the modalities and the duration of follow-up for consultation can be defined, which will help clinicians to anticipate the follow-up and to inform the parents about the duration of follow-up.

TRAb and TSH were independent predictors and can be used to perform a NH screening. TRAb levels between days 0 and 5 of life are a good predictor of HN[28] and children positive for TRAb should be monitored closely until total clearance of the maternal antibodies. In contrast, in nonimmune NH, TRAb loses its relevance as a predictor. Finally, TSH levels between days 3 and 7 remain a robust predictor of NH of all etiologies.

The strength of our study is that we found the TSH cutoff in screening for NH at the presymptomatic stage of the disease. All newborns with a TSH of less than 0.90 mIU/L should be examined by a pediatrician. If needed, early therapeutic care is essential to avoid cardiac and neurologic complications. The retrospective nature of our study limits the applicability of these results to the general pediatric population. Additional studies are needed to confirm the lower TSH cutoff at 0.90 mIU/L. The next step will be the modification of the present TSH test and the introduction of the lower TSH limit. In this way, in the future, it will be possible to screen for NH as well as neonatal hypothyroidism through a single TSH test. This finding demonstrates the relevance of our study in terms of public health. ■

Delphine Mitanchez, Alexandra Benachi, Valérie Biran, Mostafa Mokhtari, Claire Boithias, Valérie Champion, Luc Desfrere, Yves Ville, Pierre-Henri Jarreau, Marc Dommergues, Frederic Brioude and Laurent Mandelbrot participated in data collection and approved the final manuscript.

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Appendix

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