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Study of the Factors Leading to Fetal and Neonatal Dysthyroidism in Children of Patients With Graves Disease

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Context: Neonatal hyperthyroidism was first described in 1912 and in 1964 was shown to be linked to transplacental passage of maternal antibodies. Few multicenter studies have described the perinatal factors leading to fetal and neonatal dysthyroidism.

Objective: To show how fetal dysthyroidism (FD) and neonatal dysthyroidism (ND) can be predicted from perinatal variables, in particular, the levels of anti-thyrotropin receptor antibodies (TRAbs) circulating in the mother and child.

Design and Patients: This was a retrospective multicenter study of data from the medical records of all patients monitored for pregnancy from 2007 to 2014.

Setting: Among 280,000 births, the medical records of 2288 women with thyroid dysfunction were selected and screened, and 417 women with Graves disease and positive for TRAbs during pregnancy were included.

Abbreviations: aOR, adjusted odds ratio; ATD, antithyroid drug; AUC, area under receiver operating characteristic curve; CI, confidence interval; FD, fetal dysthyroidism; FT3, free triiodothyronine; FT4, free thyroxine; IgG, G protein-coupled receptors for polypeptide hormone; LT4, levothyroxine; ND, neonatal dysthyroidism; NH, neonatal hyperthyroidism; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; TH, thyroid hormone; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone.

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Results: Using the maternal TRAb levels, the cutoff value of 2.5 IU/L best predicted for FD, with a sensitivity of 100% and specificity of 64%. Using the newborn TRAb levels, the cutoff value of 6.8 IU/L best predicted for ND, with a sensitivity of 100% and a specificity of 94%. In our study, 65% of women with a history of Graves disease did not receive antithyroid drugs during pregnancy but still had infants at risk of ND.

Conclusions: In pregnant women with TRAb levels ≥2.5 IU/L, fetal ultrasound monitoring is essential until delivery. All newborns with TRAb levels ≥6.8 IU/L should be examined by a pediatrician with special attention for thyroid dysfunction and treated, if necessary.

Freeform/Key Words: Graves disease, neonatal dysthyroidism, perinatal therapy

Neonatal hyperthyroidism (NH) was first described by White in 1912 [1] and in 1964 was shown to be linked to transplacental passage of maternal antibodies [2]. Graves disease occurs in an estimated 0.1% to 0.4% of pregnant women [3–6] and 1% to 10% of the children born from these pregnancies present with hyperthyroidism [7]. Untreated, this rare and severe disease has a fetal and neonatal mortality rate of 16% to 25% [8]. Thyroid hormones (THs) play an essential role in ensuring the normal development of the fetus, particularly, the central nervous system [9, 10]. Both fetal hypo- and hyperthyroidism can potentially affect the growth of fetuses and neonates. However, fetal hypothyroidism seems to be a more severe condition in terms of fetal mental development [11], although a recent study reported that high thyroxine levels could also jeopardize the brain development of offspring [12].

THs are essential for adaptation to extrauterine life, including lung fluid and development control, adaptive thermogenesis, and a diverse range of metabolic processes in the liver, including gluconeogenesis. THs are important regulators of cardiac gene expression, and many of the cardiac manifestations of thyroid dysfunction are associated with alterations in free triiodothyronine (FT3)-mediated gene expression. The clinical manifestations of fetal and neonatal hyperthyroidism are dominated by the effects of THs on the heart and cardiovascular system. Excessive TH production has contrasting effects on the cardiovascular system. Hyperthyroidism produces a decrease in systemic vascular resistance but increases in cardiac output, heart rate, and intravascular blood volume [13]. The result is a risk of fetal death by congestive heart failure and an excess of intrauterine growth restriction and preterm delivery [4–6].

Anti-thyrotropin receptor antibodies (TRAbs) are a family of G protein-coupled receptors for polypeptide hormones (IgG) that can cross the placenta and have an effect on the fetal thyroid from 15 weeks of gestation when the IgG concentration is low and begins to increase progressively. At the 30th week of development, the fetal TRAb level is almost equal to that of the mother. A positive correlation exists between a high level of maternally transmitted antibodies and the appearance of signs of hyperthyroidism in the fetus, which explains why fetal hyperthyroidism develops during the second half of pregnancy and in mothers with a high antibody level [14]. In most cases, TRAbs have a stimulating effect; however, in rare cases, their action can be inhibitory [15].

Synthetic antithyroid drugs (ATDs) such as propylthiouracil and carbimazole cross the placenta and are responsible for the blockade of fetal thyroid hormonogenesis. The risk of hypothyroidism is likely dose-dependent. Propylthiouracil is preferred because it is less teratogenic and acts faster by blocking the peripheral conversion of FT4 to FT3. However, from the second trimester, given the risk of hepatotoxicity, a shift to carbimazole should be considered [16–18].

The management of thyroid dysfunction during pregnancy affected by Graves disease consists of monitoring the fragile balance between the risk of fetal hypothyroidism (through the excessive placental transfer of maternal ATDs) and the risk of fetal hyperthyroidism (through the placental transfer of maternal TRAbs).

The aim of the present study was to establish how to predict fetal and neonatal dysthyroidism from perinatal variables, in particular, from the TRAb levels in the mother and neonate.

1. Methods

A. Study Design and Patients

We performed a retrospective multicenter study using on data from the medical records of all patients monitored for pregnancy from 2007 to 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, and Pitié-Salpêtrière). Women with Graves disease who were positive for TRAbs at least once during pregnancy were included.

The Paris Nord Evaluation and Research Committee of Biomedical Research Projects (CEERB Paris Nord, authorization no. 13-066), the Consulting Committee on Information Processing in Health Research (authorization no. 13.296), and the French Data Protection Authority (authorization no. 6IZ084649b) approved the study protocol.

A list of pregnant women with a thyroid disease who had been followed up in the study departments from 1 January 2007 to 1 January 2014 was provided by the medical information department of each hospital. To select patients for the study, we used the "International Classification of Diseases, 10th revision, Clinical Modification" code O99.2 (endocrine, nutritional and metabolic diseases, complicating pregnancy and delivery), as Diagnosis Related Group as follows: E05 (thyrotoxicosis, hyperthyroidism), E05.0 (thyrotoxicosis with goiter), E05.4 (false thyrotoxicosis), E05.5 (thyrotoxicosis acute fit), E05.8 (other thyrotoxicosis), E05.9 (thyrotoxicosis, unspecified), E06.0 (acute thyroiditis), O90.5 (postpartum thyroiditis), E06.1 (subacute thyroiditis), E06.2 (chronic thyroiditis with transitory thyrotoxicosis), E06.3 (autoimmune thyroiditis), E06.9 (thyroiditis, unspecified), and P72.1 (neonatal hyperthyroidism). Next, we screened the medical records of these patients to select those presenting with Graves disease who were positive for TRAbs (>1 IU/L) at least once during pregnancy.

When ATD or levothyroxine (LT4) treatment was necessary, we closely monitored our patients (monthly if in steady state or every 15 days, or more frequently, if required, the in case of an imbalance) using clinical and/or biological assessments.

B. Clinical Data

A newborn was declared small for gestational age when their weight was less than the 10th percentile on the Association des Utilisateurs de Dossiers Informatisés en Périnatalogie, Obstétrique et Gynécologie curves using sex, gestational age, and the child's weight at birth.

Fetal thyroid hypertrophy was defined as a thyroid size greater than the 95th percentile on ultrasound imaging beginning at 22 weeks of gestation and repeated monthly [19].

Fetal hyperthyroidism was defined by the presence of fetal thyroid hypertrophy with at least one of the following ultrasound signs: heart rate >160 beats per minute (tachycardia), central thyroid vascularization, congestive heart failure, hydrops, or advanced bone age [20] or confirmed by fetal blood sampling or the success of the appropriate treatment.

Fetal hypothyroidism was defined by the presence of fetal thyroid hypertrophy with at least one of the following ultrasound signs: peripheral thyroid vascularization, delayed bone maturation, or increased and jerky movements or confirmed by fetal blood sampling or by the success of the appropriate treatment.

We defined fetal dysthyroidism (FD) as the presence of fetal hyper- or hypothyroidism.

Neonatal dysthyroidism (ND) was defined as the presence of ultrasound findings of thyroid hypertrophy with clinical signs of NH (tachycardia, heart failure, pulmonary arterial hypertension, hyperexcitability, poor weight gain despite appropriate daily intake, vomiting, diarrhea, craniosynostosis) [21] or clinical signs of neonatal hypothyroidism (hypothermia,

macroglossia, wide posterior and anterior fontanels, generalized hypotonia, bradycardia) confirmed by biochemical data between day 0 (cord blood at delivery) and day 7 (peripheral blood).

We estimated that the presence of neonatal thyroid hypertrophy on ultrasound scans (which has not been well standardized) without any other clinical or biochemical signs was not a clinically important form of ND.

C. Biochemical Data

TRAbs were measured using a second-generation human assay with TRAbs [TRAK; human recombinant thyroid-stimulating hormone (TSH) receptor h-TBII assay; B.R.A.H.M.S. Diagnostica, Berlin, Germany]. TRAbs were detected when their concentration was >1 IU/L. No discrepant results necessitated studies of TRAb activity [22]. The peak TRAb level was defined as the maximum value measured for each patient during pregnancy.

We assumed a biochemical imbalance was present during pregnancy if one of the three test (FT3, FT4, and TSH) levels remained outside the normal range (3 to 11 pmol/L, 10 to 26 pmol/L, and 0.2 to 4 mIU/L, respectively)[23] despite treatment. The 2.5th and 97.5th percentiles of cord blood TH levels after 36 weeks of gestation at delivery were as follows: FT3, 1.5 to 3.5 pmol/L; FT4, 10.4 to 16.6 pmol/L; and TSH, 2.6 to 11.8 mIU/L [24]. The 2.5th and 97.5th percentiles of TH levels of the newborns from days 1 to 30 of life were as follows: FT3, 1.8 to 10.4 pmol/L; FT4, 10.9 to 34.5 pmol/L [25]; and TSH, 1.8 to 9.7 mIU/L [26].

Neonatal biochemical hyperthyroidism was defined by a TSH level less than the 2.5th percentile and a FT4 level greater than the 97.5th percentile at 0 to 7 days of life. Neonatal biochemical hypothyroidism was defined by a TSH level greater than the 97.5th percentile and a FT4 level less than the 2.5th percentile at 0 to 7 days of life [8].

D. Statistical Analysis

Categorical variables were compared using χ^2 tests (or Fisher's exact test if small numbers were expected) and continuous variables using Students t test (or the Wilcoxon test in the case of non-normality). The demographic and clinical characteristics were summarized at baseline as counts and percentages relative to fetal and neonatal thyroid status, mean ± standard deviation for normally distributed continuous variables, and median and interquartile range for other continuous variables (Tables 1 and 2). A P value of <0.05 was considered statistically significant. The optimal TRAb cutoff was chosen from the lowest value giving 100% sensitivity. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed to predict FD and ND in all the women, those receiving ATDs during pregnancy, and those not receiving ATDs during pregnancy. Areas under the receiver operating characteristic (AUC) curves were calculated using univariate logistic models. We used univariate logistic regression to evaluate the relative contribution of the maternal TRAb rate and neonatal TRAb rate in the development of FD and ND (Tables 3 and 4). We estimated the odds ratio (OR) and 95% confidence intervals (CIs) to measure the association between the potential predictors and the development of FD and ND. Potential confounders or cofactors were added in a multivariate logistic regression analysis ($\alpha = 0.05$), and adjusted OR (aOR) and 95% CIs were compared with the unadjusted OR and 95% CIs. The multivariate prediction model included only four variables (peak TRAb level, ATD use, biochemical imbalance, total thyroidectomy) or three variables (TRAb level between days 0 to 5, biochemical imbalance, fetal thyroid hypertrophy) to account for the limited number of positive cases (n = 46 and n = 25, respectively; Tables 5 and 6). The variables included in the multivariate model were chosen if statistically significant and of clinical relevance. A goodness-of-fit test for continuous variables (maternal TRAb level and TRAb level between days 0 to 5) was assessed using the Hosmer-Lemeshow statistic. All data were processed using STATA, version 13, software (StataCorp, College Station, TX).

Table 1. Maternal Characteristics Stratified by Antenatal Thyroid Status

	Fetal Thyroid Hypertrophy		
Variable	**Yes (n = 46)**	**No (n = 371)**	**Unconnected *P* Value**
Maternal age, y	31.3 ± 3.9	33.6 (4.9)	0.002[a]
Parity, n	1.8 ± 1.2	1.9 (1.2)	0.78[a]
Maternal MaxTRAb, IU/L	14.2 (5.9–37.6)	1.7 (1.3–3.7)	<0.0001[b]
Maternal MaxTRAb group, IU/L			<0.0001[c]
1–10	18 (39.1)	337 (90.8)	
10–20	10 (21.7)	24 (6.5)	
20–40	8 (17.4)	5 (1.3)	
≥40	10 (21.8)	5 (1.4)	
Maternal levothyroxine	13 (28.3)	162 (43.7)	0.05[c]
Maternal ATD treatment	40 (87)	105 (28.3)	<0.0001[c]
Maternal biochemical imbalance	26 (56.6)	26 (7)	<0.0001[d]
Maternal total thyroidectomy	5 (10.9)	122 (32.9)	0.002[d]
Male sex	24 (52.2)	197 (53)	0.91[d]
Birth weight, g	2926.8 ± 640.5	3107.3 ± 651.3	0.08[a]
SGA	13 (28.3)	56 (15.1)	0.02[d]
FT3 cord blood, pmol/L	4.5 ± 3.6 (n = 35)	3.6 ± 2.3 (n = 78)	0.09[a]
FT4 cord blood, pmol/L	17.9 ± 8.4 (n = 38)	15.2 = 4.3 (n = 84)	0.02[a]
TSH cord blood, mU/L	4.4 ± 5.9 (n = 39)	7.3 ± 6.3 (n = 85)	0.01[a]
FT3, D3–D7, pmol/L	7.9 ± 5.6 (n = 42)	6.2 ± 1.9 (n = 292)	<0.0001[a]
FT4, D3–D7, pmol/L	33.0 ± 17.0	23.4 ± 9.6	<0.0001[a]
TSH, D3–D7, mU/L	2.9 ± 5.1	6.3 ± 4.4	<0.0001[a]
TRAb, D0–D5, IU/L	8.9 (1.9–19.0)	0.9 (0.9–1.3)	<0.0001[b]
TRAb group, D0–D5, IU/L			<0.0001[c]
<1	4 (8.7)	265 (71.4)	
1–10	20 (43.5)	92 (24.8)	
≥10	22 (47.8)	14 (3.8)	

Data presented as n (%) relative to fetal thyroid status, mean ± standard deviation for normally distributed continuous variables, and median (interquartile range) for other continuous variables.
Abbreviations: D, day; MaxTRAb, maximum TRAb; SGA, small for gestational age.
[a]Student *t* test.
[b]Wilcoxon test.
[c]Fisher's exact test.
[d]χ^2 test.

2. Results

Of 280,000 births, the medical records of 2288 women with thyroid dysfunction were selected and screened, and 417 women with Graves disease and positive for TRAbs during pregnancy (estimated prevalence of Graves disease, 0.15%) were included.

All 417 women had undergone at least one fetal echography centered on the fetal thyroid. Among these women evaluated for potential fetal dysthyroidism, 76 underwent second line-focused echography.

Of the 417 women, 145 (34.8%) had active disease (received ATDs during pregnancy), 157 (37.6%) were in remission (received LT4 during pregnancy; 26 had received iodine-131 therapy, 127 had undergone total thyroidectomy, and 4 had undergone partial thyroidectomy, as assessed by their medical or surgical report). Finally, 115 women (27.6%) were in remission without any treatment. Of the 52 women with a biochemical imbalance, 18 had been taking both ATDs and LT4 during pregnancy.

Of the 417 patients, 144 (34.7%) had had only one TRAb determination, 168 (40.3%) had two determinations, 63 (15.1%) had three, and 42 (9.9%) had more than three. In 98.2% of cases, the first value of TRAb was the highest.

Of these 417 pregnant women, 52 (12.5%) had fetuses or newborns that displayed dysthyroidism; 46 fetuses (11.0%) had thyroid hypertrophy, 25 newborns (6.0%) developed clinical ND, and only 19 children (4.6%) received therapy.

Table 2. Maternal Characteristics Stratified by Neonatal Thyroid Status

Variable	Neonatal Dysthyroidism		Unconnected *P* Value
	Yes (n = 25)	No (n = 392)	
Maternal age, y	30.8 (5.1)	33.5 (4.8)	0.007[a]
Parity, n	1.4 (0.8)	1.9 (1.2)	0.02[a]
Maternal MaxTRAb, IU/L	50.0 (17.3–102.0)	1.8 (1.3–4.4)	<0.0001[b]
Maternal MaxTRAb group, IU/L			<0.0001[c]
1–10	2 (8.0)	350 (89.3)	
10–20	6 (24.0)	30 (7.7)	
20–40	3 (12.0)	9 (2.3)	
≥40	14 (56.0)	3 (0.7)	
Maternal TSH, mU/L	0.8 ± 1.7	1.1 ± 1.6	0.33[a]
Maternal levothyroxine	8 (32.0)	167 (42.6)	0.29[c]
Maternal ATD treatment	20 (80.0)	125 (31.9)	<0.0001[c]
Maternal biochemical imbalance	16 (64.0)	36 (9.2)	<0.0001[d]
Maternal total thyroidectomy	6 (24.0)	121 (30.9)	0.47[d]
Male sex	14 (56.0)	202 (52.8)	0.76[d]
Birth weight, g	2771.6 ± 620.9	3107.5 ± 649.2	0.01[a]
SGA	8 (32.0)	61 (15.5)	0.03[d]
FT3 cord blood, pmol/L	5.8 ± 4.5 (n = 18)	3.5 ± 2.2 (n = 96)	0.002[a]
FT4 cord blood, pmol/L	17.7 ± 9.6 (n = 18)	17.3 ± 17.3 (n = 105)	0.50[a]
TSH cord blood, mU/L	1.7 ± 3.4 (n = 18)	7.3 ± 6.4 (n = 107)	0.0003[a]
FT3, D3–D7, pmol/L	9.8 ± 7.5 (n = 20)	6.2 ± 2.0 (n = 317)	<0.0001[a]
FT4, D3–D7, pmol/L	38.7 ± 20.5	23.6 ± 9.5	<0.0001[a]
TSH, D3–D7, mU/L	1.3 ± 4.0	6.2 ± 4.5	<0.0001[a]
TRAb, D0–D5, IU/L	24.0 (11.3–41.0)	0.9 (0.9–1.5)	<0.0001[b]
TRAb group, D0–D5, IU/L			<0.0001[c]
<1	0 (0.0)	266 (69.9)	
1–10	5 (20)	111 (28.3)	
≥10	20 (80)	15 (3.8)	

Data presented as n (%) relative to fetal thyroid status, mean ± standard deviation for normally distributed continuous variables, and median (interquartile range) for other continuous variables.
Abbreviations: D, day; MaxTRAb, maximum TRAb; SGA, small for gestational age.
[a]Student *t* test.
[b]Wilcoxon test.
[c]Fisher's exact test.
[d]χ^2 test.

Of the 46 cases of fetal thyroid hypertrophy, 23had no other signs and 8 required cordocentesis for an accurate diagnosis; 34 fetuses were hypothyroid and 12 were hyperthyroid. All cases of fetal hypothyroidism were related to maternal overtreatment with ATDs. Children with ND had a significantly lower birth weight (mean, 2771 g vs 3107 g; $P = 0.01$; Table 2) but not those with fetal thyroid hypertrophy ($P = 0.07$; Table 1).

Multivariate regression analysis revealed that the TRAb level in the mother and child was the strongest independent predictor of FD and ND (Tables 5 and 6). The expected frequencies were not significantly different from the observed frequencies using the Hosmer-Lemeshow test ($P = 0.84$ for TRAb level at days 0 to 5; $P = 0.76$ for maternal TRAb level).

Concerning FD (fetal thyroid hypertrophy), the risk was increased by a maternal hormonal imbalance (aOR, 3.7; 95% CI, 1.6 to 42.0; $P = 0.003$). Although reduced on univariate analysis, it was not independently influenced by thyroidectomy before pregnancy (aOR, 0.6; 95% CI, 0.1 to 2.8). The risk of FD was greater for the patients receiving ATDs during pregnancy (aOR, 7.6; 95% CI, 2.2 to 26.6; $P < 0.001$). Having FD increased the risk of the later development of ND (aOR, 8.4; 95% CI, 1.7 to 42.0; $P < 0.01$; Table 6).

The optimal TRAb cutoff was searched to detect FD or ND in the three populations of patients (Tables 3 and 4). In the population of all women, using the maternal TRAb level, the optimal cutoff value for predicting fetal thyroid hypertrophy was 2.5 IU/L (sensitivity, 100%;

Table 3. Relationship Between Fetal Thyroid Hypertrophy and Maternal TRAb Level

Maternal MaxTRAb	Optimal Cutoff, IU/L	Sensitivity, %	Specificity,%	PPV, %	NPV, %	Correctly Classified, %	AUC
All women (n = 417)	2.5	100 (100–100)	64 (60–68)	26 (22–30)	100 (100–100)	68	0.91 (0.87–0.94)
Receiving ATDs during pregnancy							
Yes (n = 145; 35.0%)	2.5	100 (100–100)	39 (31–47)	38 (30–46)	100 (100–100)	40	0.83 (0.76–0.90)
No (n = 272; 65.0%)	2.5	100 (100–100)	73 (68–78)	8 (5–11)	100 (100–100)	74	0.91 (0.87–0.94)

Data in parentheses are 95% confidence intervals.
Abbreviation: MaxTRAb, maximum TRAb.

specificity, 64%; PPV, 26%; NPV, 100%; AUC, 0.91; Table 3). The optimal cutoff for predicting ND was 5.9 IU/L (sensitivity, 100%; specificity, 82%; PPV, 26%; NPV, 100%; AUC, 0.97). Using the newborn TRAb level (either cord blood at delivery or peripheral blood sampling between days 0 and 5), the optimal cutoff value was 6.8 IU/L for predicting ND (sensitivity, 100%; specificity, 94%; PPV, 50%; NPV, 100%; AUC, 0.98; Table 4).

In the population of women receiving ATDs during pregnancy, using the maternal TRAb level, the optimal cutoff value for predicting fetal thyroid hypertrophy was 2.5 IU/L (sensitivity, 100%; specificity, 39% PPV, 38% NPV, 100%; AUC, 0.83; Table 3). The optimal cutoff value was 5.9 IU/L for detecting ND (sensitivity, 100%; specificity, 61%; PPV, 29%; NPV, 100%; AUC, 0.93). Using the newborn TRAb level (either cord blood at delivery or peripheral blood sampling at days 0 to 5), the optimal cutoff value was 6.8 IU/L for predicting ND (sensitivity, 100%; specificity, 89%; PPV, 59%; NPV, 100%; AUC, 0.97; Table 4).

In the population of women not receiving ATDs during pregnancy, using the maternal TRAb level, the optimal cutoff value for predicting fetal thyroid hypertrophy was 2.5 IU/L (sensitivity, 100%; specificity, 73%; PPV, 8%; NPV, 100%; AUC, 0.91; Table 3). The optimal cutoff value for predicting ND was 5.9 IU/L (sensitivity, 100%; specificity, 92%; PPV, 19%; NPV, 100%; AUC, 0.99). Using the newborn TRAb level (either cord blood at delivery or peripheral blood sampling at days 0 to 5), the optimal cutoff value was 6.8 IU/L for predicting ND (sensitivity, 100%; specificity, 96%; PPV, 31%; NPV, 100%; AUC, 0.98; Table 4).

3. Discussion

Fetal and neonatal thyroid dysfunction can occur during maternal Graves disease. Fetal hyperthyroidism can result from stimulation of TRAbs and fetal hypothyroidism from the action of ATDs. In some cases, one can even observe successive fetal hyper- and hypothyroidism

Table 4. Relationship Between Neonatal Dysthyroidism and Predictor Variable (Maternal or Neonatal TRAb Level)

Predictor Variable	Optimal Cutoff, IU/L	Sensitivity, %	Specificity,%	PPV, %	NPV, %	Correctly Classified %	AUC
All women (n = 417)							
Maternal MaxTRAb	5.9	100 (100–100)	82 (78–86)	26 (22–30)	100 (100–100)	83	0.97 (0.95–0.99)
Neonatal TRAb, D0–D5	6.8	100 (100–100)	94 (92–96)	50 (45–55)	100 (100–100)	92	0.98 (0.97–0.99)
Receiving ATDs during pregnancy							
Yes (n = 145; 35.0%)							
Maternal MaxTRAb	5.9	100 (100–100)	61 (53–69)	29 (22–36)	100 (100–100)	66	0.93 (0.87–0.98)
Neonatal TRAb, D0–D5	6.8	100 (100–100)	89 (84–94)	59 (51–67)	100 (100–100)	90	0.97 (0.94–0.99)
No (n = 272; 65.0%)							
Maternal MaxTRAb	5.9	100 (100–100)	92 (89–95)	19 (15–23)	100 (100–100)	92	0.99 (0.97–1.0)
Neonatal TRAb, D0–D5	6.8	100 (100–100)	96 (94–98)	31 (25–37)	100 (100–100)	96	0.99 (0.99–1.0)

Data in parentheses are 95% confidence intervals.
Abbreviation: MaxTRAb, maximum TRAb.

Table 5. Risk Factors for Development of Fetal Thyroid Hypertrophy According to Univariate and Multivariate Logistic Regression Model Analyses (All Women; n = 417)

	Univariate Analysis		Multivariate Analysis	
Predictor Variable	**OR (95% CI)**	***P* Value**	**aOR (95% CI)**	***P* Value**
Maternal MaxTRAb, IU/L	1.07 (1.04–1.09)	<0.0001	1.04 (1.02–1.06)	<0.0001
Maternal ATD treatment	28.96 (8.51–34.96)	<0.0001	7.61 (2.18–26.61)	<0.001
Maternal biochemical imbalance	16.89 (6.95–41.02)	<0.0001	3.76 (1.59–8.91)	0.003
Maternal total thyroidectomy	0.25 (0.09–0.65)	0.004	0.55 (0.11–2.78)	0.47
AUC	0.91 (0.87–0.94)		0.91 (0.68–1.00)	

Abbreviation: MaxTRAb, maximum TRAb.

(principally by modification of ATD administration). Neonatal hypothyroidism can be immediate (as the result of the fetal state) or delayed (when the newborn treated by ATDs switches to hypothyroidism after hyperthyroidism). All these situations can potentially jeopardize fetal and neonatal outcomes with varying degrees of severity.

When treating a patient with Graves disease at the beginning of pregnancy, one of the main issues is the prediction of FD and ND. The TRAb levels in the mother are one of the main predictors because their action can directly activate the fetal or neonatal thyroid gland or indirectly induce fetal hypothyroidism because relative overtreatment of the mother will induce fetal hypothyroidism.

Ultrasound monitoring of the fetal thyroid gland can be used to detect FD but has been limited in two ways. First, as yet, no robust data have been available to define a TRAb cutoff above which this monitoring could be considered mandatory. Second, we lacked the tools to predict NH (the most threatening neonatal situation) when the neonate still has circulating TRAbs and is no longer exposed to transplacental ATD administration. This question is of utmost importance because it will define to which facility the mother should be referred for delivery.

Our study has defined TRAb levels that indicate a need for closer assessment for FD (2.5 IU/L in maternal blood) and ND (5.9 IU/L in maternal blood) and 6.8 IU/L between days 0 and 5 in neonatal blood (Tables 3 and 4). Clavel *et al.* [27] determined a first-generation TRAb threshold of approximately 40 IU/L (normal range, <10 IU/L) for the prediction of NH. However, their study had too few patients to yield a reliable predictive value [27]. Nonetheless, their findings showed the possibility of determining the best TRAb cutoff values for the prediction of ND. Recent studies have also used second-generation TRAbs (normal range, <1.5 IU/L). Abeillon-du Payrat *et al.* [28] recently established, in a smaller series of patients with Graves disease, that a cutoff value of 5 IU/L for second-generation TRAb measurements predicted fetal hyperthyroidism with great sensitivity. However, they noted that their results should be confirmed in larger series [28].

We determined in TRAb-positive patients, the optimal cutoff values for the risk of FD and ND in three clinical situations: for patients with TRAbs, irrespective of ATD treatment; for

Table 6. Risk Factors for Development of Neonatal Dysthyroidism According to Univariate and Multivariate Logistic Regression Model Analyses (All Women; n = 417)

	Univariate Analysis		Multivariate Analysis	
Predictor Variable	**OR (95% CI)**	***P* Value**	**aOR (95% CI)**	***P* Value**
TRAb, D0–D5, IU/L	1.45 (1.29–1.63)	<0.0001	1.41 (1.22–1.62)	<0.0001
Maternal biochemical imbalance	17.58 (7.25–42.62)	<0.0001	2.56 (0.52–12.49)	0.24
Fetal thyroid hypertrophy	42.81 (15.79–116.08)	<0.0001	8.35 (1.66–42.03)	<0.01
AUC	0.98 (0.97–0.99)		0.97 (0.83–1.00)	

Abbreviation: D, day.

patients taking ATDs; and for patients with no need of ATDs. These cover all situations seen in TRAb-positive pregnant patients. The strength of our study was that we accounted for the prenatal and postnatal risks with a single measurement of the peak TRAb level during pregnancy. We have shown that in >98% of cases, the highest TRAb value was found in the first sample during pregnancy. Thus, considering that fetal echographic thyroid monitoring can be performed as early as 22 gestational days, we suggest, in accordance with international recommendations [5, 29], that the TRAb assessment should be performed before 22 gestational days, especially because only one sample is taken in some settings. We have anticipated all thyroid-related complications (*i.e.,* prenatal and postnatal hypothyroidism or hyperthyroidism). We can, therefore, use large PPVs and NPVs to anticipate complications using a single TRAb measurement. In most cases, the TRAb values will peak at the beginning of pregnancy (unpublished data); thus, obstetricians can be aware early of what they should advises patients about optimal pre- and postnatal care.

We have shown that, after birth, the optimal cutoff for ND using any TRAb measurement taken between days 0 and 5 is 6.8 IU/L. Therefore, all newborns with a TRAb level >6.8 IU/L should be examined by a pediatrician for thyroid dysfunction and treated if necessary. These data complete those of Besançon *et al.* [8], who concluded that TRAbs in the cord blood indicates a high risk of NH and that a rapid increase in FT4 is also predictive of this outcome.

ND developed in 25 newborns, 23 with hyperthyroidism and 2 with hypothyroidism. We did not test for NH and neonatal hypothyroidism separately because of the very small number of cases (n = 2), one of the limitations of our study. Our study design and the large number of patients involved (n = 417) did not allow us to couple the TRAb levels to their biological activity, which is rarely required. However, in routine cases, usually only TRAb measurements are performed, and this inability does not reduce the value of our results. Our study was retrospective with the participation of several centers, making it less robust and more heterogeneous. However, despite these limitations, we have made interesting conclusions for the management of thyroid dysfunction during pregnancy and ND in children of patients with Graves disease.

Thyroidectomy has the advantage of being a definitive treatment of most symptoms of Graves disease. However, although some investigators have reported decreased TRAb levels after thyroidectomy, we have shown that one-third of thyroidectomized patients have residual TRAb levels, although the activity of these TRAbs is thought to be lower owing to loss of antigen stimulation [20, 30]. The outstanding question is whether thyroidectomy has a protective effect on the fetuses of ongoing pregnancies. In contrast to the scarce data available [31], we have shown on univariate analysis that thyroidectomy before pregnancy protects against the occurrence of fetal thyroid hypertrophy but not against ND. Also, this "protective effect" disappeared after adjustment by multivariate analysis. Without the maternal thyroid gland, ATDs will not interfere with the fetal thyroid state, as long as ATDs are not deemed necessary because of the action of TRAbs, and we can expect that thyroidectomy will lower the risk of biochemical imbalance in the mother. However, a precise benefit/risk ratio for prophylactic thyroidectomy should now be determined. At the least, maternal thyroidectomy would avoid first-trimester embryo and fetal exposure to ATDs (teratogenicity) and risk of propylthiouracil-induced hepatotoxicity in the mother.

In conclusion, the risk of FD and ND increases with maternal hormonal imbalance and is also greater in the patients receiving ATDs during pregnancy. In our study, 65.0% of women with a history of Graves disease did not receive ATDs during pregnancy but were still at risk of ND. We have clearly shown in a large number of cases that precise TRAb cutoffs can be used to establish the best perinatal follow-up and that fine tuning of the mother's thyroid status and ultrasound monitoring of the fetal thyroid should be used to avoid or predict for FD or ND.

Acknowledgments

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References and Notes

1. White C. A foetus with congenital hereditary Graves' disease. *J Obstet Gynaecol Br Emp*. 1912;**21**: 231–233.
2. McKenzie JM. Neonatal Graves' disease. *J Clin Endocrinol Metab*. 1964;**24**:660–668.
3. Polak M, Legac I, Vuillard E, Guibourdenche J, Castanet M, Luton D. Congenital hyperthyroidism: the fetus as a patient. *Horm Res*. 2006;**65**(5):235–242.
4. Lao TT. Thyroid disorders in pregnancy. *Curr Opin Obstet Gynecol*. 2005;**17**(2):123–127.
5. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2012;**97**(8):2543–2565.
6. Weetman AP. Graves' disease. *N Engl J Med*. 2000;**343**(17):1236–1248.
7. Laurberg P, Nygaard B, Glinoer D, Grussendorf M, Orgiazzi J. Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association. *Eur J Endocrinol*. 1998;**139**(6):584–586.
8. Besançon A, Beltrand J, Le Gac I, Luton D, Polak M. Management of neonates born to women with Graves' disease: a cohort study. *Eur J Endocrinol*. 2014;**170**(6):855–862.
9. Fisher DA, Klein AH. Thyroid development and disorders of thyroid function in the newborn. *N Engl J Med*. 1981;**304**(12):702–712.
10. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. *N Engl J Med*. 1994;**331**(16): 1072–1078.
11. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;**341**(8):549–555.
12. Korevaar TIM, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, Steegers EA, Visser TJ, White T, Tiemeier H, Peeters RP. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;**4**(1):35–43.
13. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. *N Engl J Med*. 2001;**344**(7): 501–509.
14. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid*. 1992;**2**(2):155–159.
15. Ohira S, Miyake M, Kobara H, Kikuchi N, Osada R, Ashida T, Hirabayashi K, Nishio S, Kanai M, Shiozawa T. Fetal goitrous hypothyroidism due to maternal thyroid stimulation-blocking antibody: a case report. *Fetal Diagn Ther*. 2010;**28**(4):220–224.
16. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, Laurberg P, McDougall IR, Montori VM, Rivkees SA, Ross DS, Sosa JA, Stan MN; American Thyroid Association; American Association of Clinical Endocrinologists. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Thyroid*. 2011;**21**(6):593–646.
17. Masiukiewicz US, Burrow GN. Hyperthyroidism in pregnancy: diagnosis and treatment. *Thyroid*. 1999; **9**(7):647–652.
18. Rosenfeld H, Ornoy A, Shechtman S, Diav-Citrin O. Pregnancy outcome, thyroid dysfunction and fetal goitre after in utero exposure to propylthiouracil: a controlled cohort study. *Br J Clin Pharmacol*. 2009; **68**(4):609–617.
19. Huel C, Guibourdenche J, Vuillard E, Ouahba J, Piketty M, Oury JF, Luton D. Use of ultrasound to distinguish between fetal hyperthyroidism and hypothyroidism on discovery of a goiter. *Ultrasound Obstet Gynecol*. 2009;**33**(4):412–420.

20. Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, Noel M, Toubert ME, Léger J, Boissinot C, Schlageter MH, Garel C, Tébeka B, Oury JF, Czernichow P, Polak M. Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab*. 2005;**90**(11): 6093–6098.
21. Daneman D, Howard NJ. Neonatal thyrotoxicosis: intellectual impairment and craniosynostosis in later years. *J Pediatr*. 1980;**97**(2):257–259.
22. Villalta D, Orunesu E, Tozzoli R, Montagna P, Pesce G, Bizzaro N, Bagnasco M. Analytical and diagnostic accuracy of "second generation" assays for thyrotrophin receptor antibodies with radioactive and chemiluminescent tracers. *J Clin Pathol*. 2004;**57**(4):378–382.
23. Glinoer D, De Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejune B. Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab*. 1990;**71**(2):276–287.
24. Guibourdenche J, Noël M, Chevenne D, Vuillard E, Voluménie JL, Polak M, Boissinot C, Porquet D, Luton D. Biochemical investigation of foetal and neonatal thyroid function using the ACS-180SE analyser: clinical application. *Ann Clin Biochem*. 2001;**38**(Pt 5):520–526.
25. Kratzsch J, Schubert G, Pulzer F, Pfaeffle R, Koerner A, Dietz A, Rauh M, Kiess W, Thiery J. Reference intervals for TSH and thyroid hormones are mainly affected by age, body mass index and number of blood leucocytes, but hardly by gender and thyroid autoantibodies during the first decades of life. *Clin Biochem*. 2008;**41**(13):1091–1098.
26. Elgimer MW, Kuhnel W, Lambecht H-G, Ranke MB. Reference intervals from birth to adulthood for serum thyroxine (T4), triiodothyronine (T3), free T3, free TA, thyroxine binding globulin (TBG) and thyrotropin (TSH). *Clin Chem Lab Med*. 2001;**39**(10):973–979.
27. Clavel, S, Madec AM, Bornet H, Deviller P, Stefanutti A, Orgiazzi J. Anti TSH-receptor antibodies in pregnant patients with autoimmune thyroid disorder. *Br J Obstet Gynaecol*. 1990;**97**(11):1003–1008.
28. Abeillon-du Payrat J, Chikh K et al. Predictive value of maternal second-generation thyroid-binding inhibitory immunoglobulin assay for neonatal autoimmune hyperthyroidism. *Eur J Endocrinol*. 2014; **171**(4):451–460.
29. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Laurberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017; **27**(3):315–389.
30. Donnelly MA, Wood C, Casey B, Hobbins J, Barbour LA. Early severe fetal Graves disease in a mother after thyroid ablation and thyroidectomy. *Obstet Gynecol* 2015;**125**:1059–1062.
31. Zuppa AA, Sindico P, Perrone S, Carducci C, Antichi E, Alighieri G, Cota F, Papacci P, De Carolis MP, Romagnoli C, Cardiello V. Different fetal-neonatal outcomes in siblings born to a mother with Graves-Basedow disease after total thyroidectomy: a case series. *J Med Case Reports*. 2010;**4**:59.