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ORIGINAL ARTICLE

Characterization of children born to mothers with Graves' disease

Caracterización de recién nacidos hijos de madres portadoras de enfermedad de Graves

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What do we know about the subject matter of this study?

Neonatal hyperthyroidism can be severe if not treated early. Maternal and neonatal TRAb levels help to define management in newborns. It is important to determine predictors of this disease.

What does this study contribute to what is already known?

This is the first national case report of children born to mothers with Graves' disease. The rate of neonatal hyperthyroidism is similar to that reported in the literature. TSH levels between days 2-6 were a good predictor of disease.

Abstract

Neonatal hyperthyroidism is a disease that can cause mortality and sequelae. To date, there is no clinical series of cases that allows us to know the local reality of this condition. **Objective**: to characterize the children of mothers with Graves' disease (GD) from a clinical and biochemical point of view. **Subjects and Method:** A prospective follow-up of all newborns (NB) of mothers with history of GD was performed in two public hospitals in Santiago, during 5 years. Clinical and laboratory variables of mother-child pairs and thyroid-stimulating hormone receptor antibodies (TRAbs) levels were analyzed looking for associations between these variables and the development of neonatal hyperthyroidism. **Results:** Seventy-six mother-child pairs were included (0.2% of all deliveries). Five neonates (6.6%) presented biochemical hyperthyroidism, and 3 of them developed clinical disease and required treatment. All 5 NBs who developed hyperthyroidism had mothers with positive or indeterminate TRAbs. No child of TRAbs-negative mothers developed the disease. TRAbs could be determined in only 65% of the mothers and 72% of the NBs. There was a significant correlation between maternal TRAbs titers ($p < 0.03$), neonatal TRAbs titers ($p < 0.008$), and neonatal TSH between days 2-6 ($p < 0.006$), with the subsequent development of hyperthyroidism. All cases of neonatal hyperthyroidism were transient. There was no mortality in our series. **Conclusions:** This is the first national case series of children of mothers with GD. Maternal and neonatal TRAbs and TSH between days 2-6 of life were predictors of neonatal hyperthyroidism.

Keywords:
Neonatal Hyperthyroidism;
Neonatal Graves' Disease;
Child of Hyperthyroid Mother;
Anti-TSH Receptor Antibodies

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Introduction

Neonatal hyperthyroidism is, but it can be associated with significant morbidity and mortality. Its most frequent cause is maternal Graves' disease (GD), which affects 0.2% of pregnancies[1,2]. Other causes of neonatal hyperthyroidism are genetic variants activating thyroid-stimulating hormone (TSH) receptor or activating G protein in McCune-Albright syndrome[2,3].

During pregnancy, in women with GD, TSH receptor antibodies (TRAbs) pass through the placenta and can affect fetal and neonatal thyroid function[4,5]. TRAbs can be stimulating or inhibitory[6]. Stimulating TRAbs can cause hyperthyroidism in the fetus and newborn[1-6].

Neonatal hyperthyroidism (NH) is observed in 1-5% of newborns (NB) born to GD mothers [7-9]. Neonatal hyperthyroidism is usually transient, but in its natural history, it reaches up to 25% of mortality[1,2]. If fetal and neonatal hyperthyroidism is not treated promptly, it can cause ventricular arrhythmias, heart failure, craniosynostosis, microcephaly, and delayed psychomotor development, among other complications[1-4,7]. The importance of early detection and treatment has led to the recent publication of multiple studies and clinical guidelines[9-12]. The measurement of TRAbs in both the mother and the newborn is essential to allow the detection of NBs at greater risk of developing hyperthyroidism. The incidence of neonatal hyperthyroidism, as well as the TRAbclearance time in the newborn, has been associated with maternal and neonatal antibody titers[13]. Despite the existence of these reviews and clinical guidelines, to our knowledge, there are no clinical series describing the local reality of this pathology.

The objective of this study was to describe the clinical and laboratory aspects relevant to the presentation and clinical course of NBs born to mothers with Graves' disease.

Subjects and Method

Prospective, observational, and descriptive study of the clinical evolution and thyroid function of NBs born to mothers with Graves' disease. All NBs whose mothers had history of hyperthyroidism due to GD were included, regardless of the time since diagnosis. The clinical history of mother-child pairs was analyzed, including those born between January 2015 and January 2020, in the *Hospital San Juan de Dios* and *Hospital San Borja Arriarán*, both located in Santiago, Chile.

All NBs born to mothers with history of GD were evaluated by a neonatologist and pediatric endocrinologist within the first 5 days of life for entry into the study. The maternal clinical record was reviewed to confirm the diagnosis of GD. The following clinical variables of the mothers were recorded and analyzed: age, time since the hyperthyroidism diagnosis, use of antithyroid drugs (ATD) during pregnancy, history of surgical or radioactive iodine (RAI) treatment, and maternal pregnancy complications.

The laboratory workup evaluated the presence of TRAbs and their plasma levels during the 3rd trimester of pregnancy. It was not possible to standardize the search for fetal goiter in antenatal ultrasound scans, but the data was included if it was in the maternal record.

At birth, if the mother had no TRAbs measurement, or if these were positive in the 3rd trimester, the NB was considered at risk of developing NH, indicating the measurement of anti-TSH receptor antibodies and thyroid hormones (TSH, T3, and FT4) in peripheral blood.

All NBs were under non-invasive monitoring of heart rate (HR), blood pressure (BP), and respiratory rate (RR) until TRAbs and thyroid profile values were available.

The following clinical and auxological data of the NBs were recorded and analyzed: gestational age (GA), birth weight (BW), birth length (BL), and head circumference (HC) with their respective Z-scores according to z-tables previously validated for the Chilean population[14]. The presence of associated malformations and symptoms or complications attributable to hyperthyroidism was also evaluated. The laboratory study of the NBs included thyroid function of TSH (mIU/L), FT4 (ng/dL), and T3 (ng/mL), grouped in 4 different measurement times (2 to 6 days of life; 7 to 14 days of life; 15 to 30 days of life, and older than 30 days of life).

Finally, serum levels of TRAbs of the NBs were measured. "Positive" TRAbs were defined as any value equal to or higher than the reference value. In the case of positive TRAbs in the newborn, monitoring of TRAbs levels and thyroid function (TSH, FT4, and T3) was indicated every 2 to 4 weeks until normalization.

Thyroid hormones were measured in each hospital by chemiluminescence method, and in external laboratories using quantitative enzyme immunoassay (EIA). To homogenize the results of TRAbs measured in different centers, they were tabulated according to the number of times over the upper normal value ("xNV").

The NBs born to mothers with TRAbs (-) during the 3rd trimester were not considered to be at risk of hyperthyroidism, therefore no antibody or thyroid function were measured[9,11]. However, in those cases in which the mother received treatment with ATD during pregnancy, the thyroid function of the newborn was

evaluated during the first week of life to rule out the effect of these on neonatal thyroid function.

Two forms of neonatal hyperthyroidism were identified: the asymptomatic biochemical one (biochemical hyperthyroidism) and the symptomatic biochemical one (clinical hyperthyroidism). Biochemical NH was defined as TSH concentrations lower than p2.5 or - 2SD for gestational age and days of life, added to levels of T4, free T4, and/or T3 over p97.5 or + 2SD for gestational age and days of life[9,15-17].

The diagnosis of clinical NH was made by the treating team, based on the finding of biochemical hyperthyroidism associated with persistent or progressive tachycardia (> 180 bpm at rest), and at least two of the following clinical findings: tremor, fever, irritability, premature closure of fontanelles, poor weight gain despite adequate nutritional intake, diarrhea, goiter, or compatible findings in the thyroid ultrasound scan (increased volume and vascular flow).

Those NBs with a diagnosis or suspected NH were hospitalized in the Neonatology Unit for monitoring. The decision of pharmacological treatment, as well as the drug to be used, was at the discretion of the respective treating medical team.

Statistical analysis was performed using the IBM SPSS Statistics software. The mean, standard deviation, median, and ranges of the variables were obtained. For comparison between groups, Fisher's exact test and the U test were used for categorical variables and Student's t-test for the non-categorical ones. A $p < 0.05$ value was considered statistically significant.

The study was approved by the scientific ethics committee of both hospitals. Informed consent was requested from the parents for the review of the clinical records.

Results

76 mother-child pairs were analyzed, of which 5 NBs (6.6%) developed biochemical hyperthyroidism, and of these, 3 presented symptoms. As for the mothers, 58 of them had active hyperthyroidism at the time of delivery. The remaining 18 were being treated for hypothyroidism secondary to RAI or thyroidectomy. The mean maternal age was 30.3 ± 6.2 years, ranging from 20 to 42 years. The years elapsed since the diagnosis of hyperthyroidism were 3.1 ± 3.1 years (range 0-13 years). Eight mothers were initially diagnosed with hyperthyroidism during pregnancy. TRAbs measurement was only performed in 50 of the mothers (65.7%). There was one case of fetal goiter, which finally did not evolve to clinical hyperthyroidism. There were no reported cases of fetal hyperthyroidism. Table 1 shows the clinical description of the mothers and NBs.

Regarding maternal characteristics (TRAbs positivity and ATD use), we identified six groups of NBs (Table 2): maternal positive TRAbs and active ATD use (TRAbs +/ATD +); mothers with positive TRAbs and no ATD use (TRAbs +/ATD -); mothers with indeterminate TRAbs and no ATD use (TRAbs?/ATD -); mothers with indeterminate TRAbs and with ATD use (TRAbs?/ATD +); mothers with negative TRAbs and with ATD use (TRAbs -/ATD +); and mothers with negative TRAbs and without ATD use (TRAbs -/ATD -). Cases of neonatal hyperthyroidism occurred in the TRAbs +/ATD + (2 cases), TRAbs?/ATD + (2 cases), and TRAbs +/ATD - (1 case) groups.

The "indeterminate" TRAbs were those cases in which the test was not performed on the mother due to different reasons, including lack of financial resources, poor adherence to endocrinological and/or obstetrical check-ups, or no request by the treating physician.

Regarding the characteristics of the NBs, there were no cases of fetal or neonatal death in the study group. Two NBs presented congenital defects, one case with biochemical hyperthyroidism and esophageal atresia born to a TRAbs +/ATD - mother, and the second case an NB with cleft lip and palate born to a TRAbs?/ATD + mother. No newborn had severe heart defects, craniosynostosis, aplasia cutis congenita, or other malformations attributable to hyperthyroidism or ATD use.

A newborn developed persistent hypothyroidism and required management with levothyroxine, son of a mother with indeterminate TRAbs, and without the use of ATD due to discontinuation. This mother had poor adherence to follow-up and treatment, with active hyperthyroidism before and during pregnancy.

When grouping the NBs according to neonatal variables (TRAbs positivity and presence of hyperthyroidism), we identified 3 groups. The first group were NBs with TRAbs (-); the second one NBs with TRAbs (+) without hyperthyroidism, and the last group NBs with TRAbs (+) and hyperthyroidism. In these groups, although there is a large overlap of values, we found a significant correlation between higher maternal TRAbs titers and the development of neonatal hyperthyroidism ($p < 0.03$) (Figure 1A). NBs with hyperthyroidism were at higher risk of prematurity ($p < 0.008$). TRAbs titers (xNV) are higher in NBs developing with neonatal hyperthyroidism ($p < 0.016$) (Figure 1B). A TRAbs titer greater than 10 times the highest normal limit was a predictor factor of neonatal hyperthyroidism with 100% sensitivity, 97.2% specificity, 71.4% positive predictive value, and 100% negative predictive value.

Figure 2 shows the evolution of thyroid hormone levels in the different groups of NBs. Biochemical hyperthyroidism was present between 2-6 days of life

with suppressed TSH in 4 of 5 NBs, with a statistically significant difference with NBs with hyperthyroidism ($p < 0.006$) (Figure 2A). There was a trend to lower mean TSH levels between days 2-6 in patients with clinical hyperthyroidism than in those with biochemical hypothyroidism only (0.002 ± 0.002 vs. 0.55 ± 0.89 mIU/L). It is important to note that TSH suppression preceded the onset of symptoms in all cases of clinical hyperthyroidism, and there were no significant differences in FT4 or T3 levels between groups. A TSH between days 2-6 lower than 0.5 mIU/L was a predictor of development of neonatal hyperthyroidism with 80% sensitivity, 100% specificity, 100% positive predictive value, and 98.6% negative predictive value.

Of all the pairs analyzed, only 5 NBs (6.6%) developed biochemical hyperthyroidism, all of them with TRAbs (+) levels, and 3 of them (3.9%) developed clinical disease and were treated with ATD. Three of the NBs were preterm, and two of them were small for gestational age (SGA). All had normal length and head circumference for gestational age. Table 3 describes the clinical characteristics of the 5 cases.

Patient P1 was born in good general condition, developed jaundice requiring triple phototherapy, and, on the 3rd day of life, started persistent tachycardia over 200 bpm. Seven days after birth treatment was started with propranolol and prednisone. Due to lack of availability, methimazole was added from the 10th day of life, which normalized FT4 levels at 30 days of life. Beta-blockers and corticoids were discontinued at 16 days of life and methimazole at 2 months. Patient P2 presented normal thyroid function during the first week, but with TSH suppression and elevated FT4 from the 7th day, however, the NB remained asymptomatic throughout the hospitalization as did patient P3. Patient P4, born in good general condition, on the 4th day of life presented with irritability, tremors, and persistent and progressive tachycardia higher than 200 bpm. On the 5th day of life, treatment with methimazole and propranolol was started. Thyroid function normalized after 20 days. At 35 days of life, methimazole was discontinued. Patient P5 presents with transient tachypnea related to prematurity. On the 5th day of life, persistent tachycardia greater than 200 bpm at rest and resting tremors were observed. It was decided to start methimazole, which was discontinued by neonatology on the third day of its use. Thyroid function normalized at 47 days.

Table 1. Clinical characteristics and TRAb levels in mothers with Graves' disease and their newborns.

	Results
Maternal variables	
Mean age, years	30.3 ± 6.2
ATD use during pregnancy, n/N (%)	38/76 (50)
Radioactive Iodine use, n/N (%)	13/76 (17.1)
Thyroidectomy, n/N (%)	5/76 (6.6)
Years since diagnosis of GD	3.1 ± 3.1
TRAbs measurement (3rd Trimester)	
Performed, n/N (%)	50/76 (65.7)
Mean values, UI/l (Range)	4.0 ± 5.2 (0.36-28.0)
Positive TRAbs, n/N (%)	43/50 (86)
TRAbs, xNV	x7.1 ± 8.9
Neonatal Variables	
Gestational Age, weeks (Range)	37.8 ± 2.4 (28-41)
Full Term NB, n/N (%)	62/76 (81.6)
Preterm NB, n/N (%)	14/76 (18.4)
Birthweight, g (Range)	3.148 ± 647 (970-4.430)
AGA, n/N (%)	53/76 (69.7)
SGA, n/N (%)	13/76 (17.1)
LGA, n/N (%)	9/76 (11.8)
Birth length, cm (Range)	48.7 ± 3.4 (31.5-54.0)
Head circumference, cm (Range)	34.0 ± 2.1 (26-38)
TRAbs measurement	
Performed, n/N (%)	55/76 (72.3)
Positive TRAbs, n/N (%)	38/55 (69.1)
Mean values, UI/l	2.81 ± 3.64
TRAbs, xNV	x4.6 ± 7.5
Neonatal Hyperthyroidism, n (%)	5 (6.6%)
Biochemical Hyperthyroidism, n (%)	2 (2.6%)
Clinical Hyperthyroidism, n (%)	3 (3.9%)

NB: Newborn. AGA: Adequate for Gestational Age. SGA: Small for Gestational Age. LGA: Large for Gestational Age. ATD: Anti-thyroid Drugs. GD: Graves' disease. TRAbs: TSH Receptor Antibodies. xNV: times over the upper normal value.

Discussion

This study provides locally relevant information on the clinical evolution of NBs born to mothers with Graves' disease, which, at the same time, allows to guide and optimize the initial management of these patients.

The frequencies of pregnancies in women with GD, as well as the proportion of cases with hyperthyroidism, are in line with those reported in the literature, so it is likely that our sample adequately reflects the local situation. Between the two centers, there was an average of about 8,000 deliveries per year in the last 5 years. If we consider 76 mothers with GD in the 5 years of study, we obtain 0.19%, which is very simi-

Table 2. Description of newborns born to mothers with GD according to maternal characteristics

	TRAbs (+)		TRAbs (-)		Indeterminate TRAbs	
	TRAb+/DAT+ (n = 24)	TRAb+/DAT- (n = 20)	TRAb-/DAT+ (n = 3)	TRAb-/DAT- (n = 2)	TRAb?/DAT+ (n = 11)	TRAb?/DAT- (n = 16)
Gestational Age (median)	37	39	38	39	37	38
Preterms < 37weeks	4	1	1	0	1	2
Preterms < 32weeks	0	1	0	0	1	1
Mean Birthweight, g	3,055	3,302	3,863	2,985	2,761	3,232
AGA	20	15	1	1	6	11
SGA	2	3	0	1	4	2
LGA	2	2	2	0	0	3
Mean birth length, cm	48.3	49.3	49.7	48.8	48.3	48.8
< p10	4	1	1	0	1	1
> p90	1	1	2	0	1	2
Mean HC, cm	33.6	34.7	35.8	34.3	33.4	33.6
< p10	2	1	0	0	1	2
> p90	0	2	2	0	1	0
Mean TRAb levels UI/L	3.2	2.4	-	-	3.9	1.1
xNV	x4.42	x2.8			x10.9	x1.71
Positivity	81%	57.8%			62.5%	66.7%
Congenital defects	0	1 (atresia esofágica)	0	0	1 (fisura labiopalatina)	0
Neonatal Hyperthyroidism	2	1	0	0	2	0
ATD treatment	1	0	0	0	2	0
Hypothyroidism	0	0	0	0	0	1

NB: Newborn. AGA: Adequate for Gestational Age. SGA: Small for Gestational Age. LGA: Large for Gestational Age. HC: Head circumference. ATD: Anti-thyroid Drugs. GD: Graves' disease. TRAbs: TSH Receptor Antibodies. xNV: times over the upper normal value.

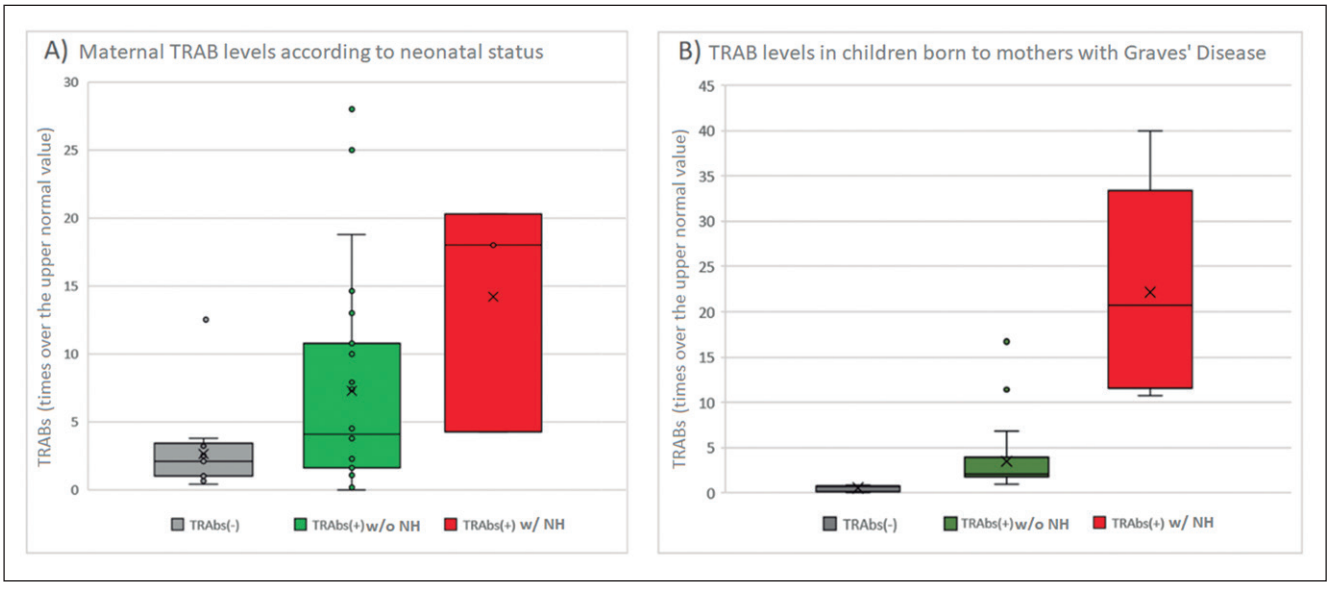

Figure 1. TRAb levels in mothers with Graves' disease and their newborns. TRAbs: TSH Receptor antibodies. NH: Neonatal Hyperthyroidism.

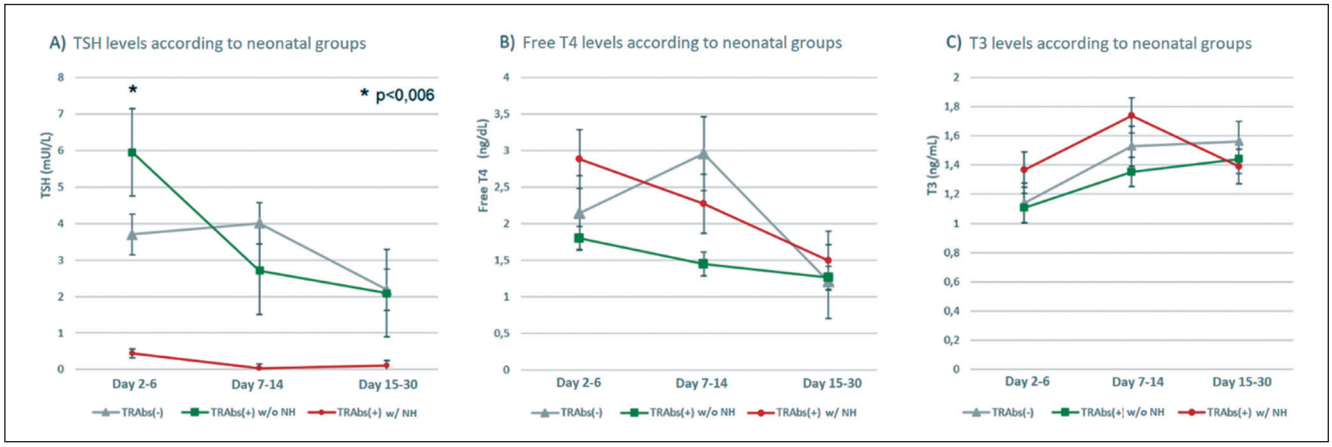

Figure 2. Thyroid hormone levels in neonates born to mothers with Graves' disease. TRAbs: TSH Receptor antibodies NH: Neonatal Hyperthyroidism.

lar to that reported in the literature[1,2,4]. On the other hand, the proportion of NBs that developed the disease was slightly higher compared with other publications (6.6% vs. 1-5.5%)[1,8,9].

As previously reported in the international literature[13,18,19], our case report demonstrated an association between maternal GD and prematurity. However, there were no significant differences in weight, length, or head circumference Z-scores, neither were cases of craniosynostosis or decreased head circumference reported in the group with hyperthyroidism; however, it is important to mention that these alterations may occur later in the follow-up of these patients.

Although esophageal atresia is a malformation classically attributed to the teratogenic effect of methimazole[20], in the case that presented this complication, the mother was not under treatment. Some studies suggest that hyperthyroidism itself would have a teratogenic effect on the gastrointestinal tract[20-22].

Regarding the other congenital malformation found, there is evidence of association of ATD with choanal atresia and some mild facial dysmorphies, but not with cleft lip and palate or other types of craniofacial malformations.

In the group of mothers with TRAbs (-), there were no cases of hyperthyroidism or altered thyroid function. This confirms the importance of determining maternal TRAbs in the 3rd trimester of pregnancy as one of the main risk factors for the development of neonatal hyperthyroidism[9,11]. Thus, NBs born to mothers with GD and TRAbs (-) in the third trimester of pregnancy do not require further study or specific

Table 3. Clinical characteristics of NB presenting with Neonatal Hyperthyroidism

	Maternal TRAbs (xNV)	Maternal ATD	GA (weeks)	TSH Day 2-6 (mUI/L)	Free T4 Day 2-6 (ng/dL)	T3 Day 2-6 (ng/mL)	NB TRAbs (xNV)	Symptoms (onset, days)	Treatment
P1	Indeterm	Metimazole	34	0.05	4.75	2.08	x40	Tachycardia (3) Jaundice (3)	Prednisone, Metimazole, Propranolol
P2	x4.25	Metimazole	37	2.1	2.46	1.07	x10.7	(-)	(-)
P3	x20.3	No	32	0.03	1.97	1.1	x12.4	(-)	(-)
P4	x18.0	Metimazole	37	0.006	2.78	1.75	x20.7	Tachycardia (4) Irritability (4) Tremor (4	Metimazole Propranolol
P5	Indeterm	Metimazole	28	0.012	2.47	0.84	x26.8	Tachycardia (5) Tremor (5)	Metimazole Propranolol

NB: Newborn. TRAbs: TSH Receptor Antibodies. xNV: times over the upper normal value. ATD: Anti-thyroid Drugs. GA: Gestational Age Antibodies.

follow-up. On the other hand, the presence of maternal TRAbs (+) in the third trimester of pregnancy increases the risk of developing neonatal hyperthyroidism, and this risk is greater as the titers of these antibodies are higher.

It is important to note that the risk of developing neonatal hyperthyroidism persists despite definitive maternal treatment (thyroidectomy or radioiodine), as was the case of an NB whose mother underwent a thyroidectomy a year earlier. For this reason, all pregnant women with history of GD should have a TRAbs determination during the 3rd trimester of pregnancy, regardless of the years that have elapsed since diagnosis or their thyroid status (hyperthyroidism or hypothyroidism due to definitive therapy with surgery or radioiodine)[8,10-12]. This shows that adequate prenatal maternal monitoring in coordination and collaboration with the obstetric and adult endocrinology teams is essential for the proper management of NBs born to mothers with GD.

All the NBs who presented neonatal hyperthyroidism had TRAbs (+) in the first week of life, presenting a statistically significant association with the titers of these antibodies, particularly when these reached values > 10xNV ($p < 0.016$). This is in line with previous studies that establish newborn TRAbs titers as one of the main prognostic factors for the development of neonatal hyperthyroidism[9].

Within the group of NBs that developed clinical hyperthyroidism, it should be noted that the onset of symptoms ranges from 3 to 7 days, with a mean of 4 days. Considering that most NBs without apparent pathology, are discharged between 48-72 hours of life, a newborn born to a mother with GD could develop neonatal hyperthyroidism at home, with underdiagnosis, lack of timely treatment, and potentially lethal complications. Therefore, it has been suggested that all NBs whose mother is a carrier of GD with TRAbs (+) in the 3rd trimester of pregnancy or with unknown TRAbs titers, should remain hospitalized during the first week of life until TRAbs and/or thyroid function are determined to rule out neonatal hyperthyroidism.

Regarding the evolution of thyroid function in NBs born to mothers with GD who developed hyperthyroidism, a significant TSH suppression within the first week of life stands out, and with no significant differences in T3 or FT4 increase compared with NBs without hyperthyroidism. According to a recently published French multicenter study[13], in addition to TRAbs levels, the measurement of thyroid hormones in the first days of life (2 to 6), had a good correlation with the later development of hyperthyroidism. Thus, in our clinical series, in all cases of clinical hyperthyroidism, there was a deep and early TSH suppression. This is particularly striking considering that the physiological response of the NB in the first days of postnatal life is to TSH increase followed by elevation of T3 and T4 that favors thermogenesis and thermoregulation necessary for adapting to extrauterine life in the first days of life[16]. For this reason, a suppressed TSH in the first week of life in an NB born to a mother with GD may be an extra risk factor for hyperthyroidism to be considered when it is not possible to measure TRAbs levels and, therefore, this NB should be strictly monitored. This finding may have implications in clinical practice, given the difficulty in measuring TRAbs promptly in public hospitals.

Despite providing relevant information at the national level, our research has several limitations. The sample size was small since this condition is not very prevalent. The most feasible way to increase the number of cases is to perform multicenter studies, but this increases the heterogeneity of the data and diagnostic and management criteria. Another important limitation is that it was not possible to measure TRAbs levels in all mothers and NBs. This test is not usually performed in hospitals of the public health system, and many times it must be paid for by the patient's family in private laboratories. This hindered the follow-up necessary to determine the clearance time of TRAbs titers in NBs. The above highlights the importance of tertiary hospital laboratories in our country being able to perform TRAbs level determinations under a standardized and validated technique, to ensure optimal management of these NBs and their mothers.

Prospective long-term follow-up studies are needed to evaluate the neurodevelopment of NBs born to mothers with Graves' disease and, especially, of those who developed clinical hyperthyroidism. All the NBs in our cohort were discharged in good condition, but we cannot conclude regarding the possible late repercussions of this disease.

The main objective of this study was to make a detailed description of the clinical presentation of children born to mothers with GD. To our knowledge, this is the first national report of a clinical series of children born to mothers with Graves' disease and, therefore, it aims to contribute with information that will allow optimizing the management of these patients in postpartum and neonatology units. The collaborative work between obstetrics, adult endocrinology, neonatology, and pediatric endocrinology units is essential for an adequate follow-up and early detection of NBs at risk of developing neonatal hyperthyroidism.

In conclusion, this study allows us to better understand the local reality of NBs born to mothers with Graves' disease. These results are consistent with those reported in the international literature and allow us to identify those NBs born to mothers with GD at risk of developing neonatal hyperthyroidism. Thus,

we can establish that NBs born to mothers with positive or indeterminate TRAbs in the 3rd trimester of pregnancy should be hospitalized to determine TRAbs and thyroid function due to the risk of neonatal hyperthyroidism. NBs born to mothers with TRAbs (-) in the 3rd trimester of pregnancy do not require study or follow-up, except to rule out hypothyroidism caused by maternal ATD use. Maternal TRAbs titers, neonatal TRAbs, and TSH measured between 2-6 days of life are useful tools to predict the development of neonatal hyperthyroidism.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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