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Short title: Hemodynamics in newborns and Graves' disease

Abstract

Purpose: Cardiac insufficiency is a major morbidity in neonatal hyperthyroidism. It is important to assess the hemodynamics in neonates born to mothers with Graves' disease (GD). This study prospectively evaluated the hemodynamic changes in neonates born to mothers with GD.

Methods: Overall, 80 newborns were enrolled. Thirty-six neonates were born to mothers with GD who were positive for thyroid-stimulating hormone (TSH) receptor antibody (TRAb), and 44 were born to mother negative for TRAb. The serum levels of TSH, free triiodothyronine (FT_3), free thyroxine (FT_4), and N-terminal-pro-B-type natriuretic peptide (NT-proBNP), the cardiac output, and cardiac index (CI) evaluated by echocardiography were compared between the two groups at several postnatal points (day of delivery and 5, 10, and 30 days of life).

Results: The TRAb-positive newborns had higher FT_4 levels and CI on Day 5 (both $p<0.05$) and higher FT_3 ($p<0.05$) and FT_4 levels ($p<0.01$) and CI ($p<0.01$) but lower TSH levels ($p<0.05$) on Day 10 than the TRAb-negative newborns. The TRAb-positive newborns had significantly higher NT-proBNP levels on Days 5 (median 752 vs. 563 pg/mL, $p=0.034$) and 10 (median 789 vs. 552 pg/mL, $p=0.002$) than the TRAb-negative newborns.

Conclusions: Hemodynamic changes in neonates born to TRAb-positive mothers with GD resulted in a higher CI and NT-proBNP levels than in those with TRAb-negative mothers from postnatal days 5 to 10.

Key words: Neonatal hyperthyroidism; Cardiac Output; N-terminal-pro-B-type natriuretic peptide; Thyroid-stimulating hormone receptor antibody; Echocardiography

Declarations

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Conflicts of interest: The authors declare no conflicts of interest.

Ethics approval: The study was conducted in accordance with the ethical principles described in the Declaration of Helsinki and was approved by the local ethics committees.

Consent to participate: Informed consent was obtained from the parents of each newborn.

Consent for publication: Not applicable.

Availability of data and material: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Code availability: Not applicable.

Authors' contributions: TI designed and conducted the research, conducted the statistical analyses, interpreted the data, and drafted the initial manuscript. HU, SI, TB, and AO made substantial contributions to the acquisition of data. SI and HI contributed to the study design and provided comments on the manuscript. All authors revised and approved the final version.

Introduction

Neonatal Graves' hyperthyroidism results from transplacental passage of stimulatory thyroid-stimulating hormone (TSH) receptor antibody (TRAb) from the mother [1-4]. Cardiac insufficiency is a major morbidity in this disease [5] and is associated with the short-term prognosis after birth. Death from congestive heart failure and arrhythmia occurs in severe cases [6]. There are reports of newborn patients with heart failure associated with neonatal hyperthyroidism [7-10]. It is therefore important to assess the hemodynamics in neonates born to mothers with GD. A few reports have evaluated hemodynamics with echocardiography and biomarkers, such as N-terminal-pro-B-type natriuretic peptide (NT-proBNP), in adult patients with thyroid disease [11-13]. However, no previous studies have measured the hemodynamics in neonates born to mothers with thyroid disease. The present study prospectively evaluated the hemodynamic changes in neonates born to mothers with Graves' disease (GD).

Materials and Methods

Subjects

The subjects of this study were neonates born to mothers with GD who became pregnant between April 2006 and May 2018 and visited Hamamatsu University Hospital. The inclusion criteria for the mothers were as follows: a past or current history of GD diagnosed by an endocrinologist based on clinical and laboratory test findings for hyperthyroidism with goiter, Graves' ophthalmopathy or dermopathy; and at least one positive test for TRAb [14, 15]. No exclusion criteria for mothers were used. The exclusion criteria for neonates were congenital heart disease, hemodynamically significant patent ductus arteriosus, and persistent pulmonary hypertension, all of which cause elevated NT-proBNP levels [16-18].

This prospective study included two groups: neonates born to mothers consistently negative for TRAb in the third trimester of pregnancy, and neonates born to mothers with at least one positive TRAb assay in the third trimester of pregnancy. For all newborns, the body height and weight and heart rate (HR) were measured on the day of delivery (Day 0) and at 5 (Day 5), 10 (Day 10), and 30 (Day 30) days of age. All newborns were followed clinically until three months of age, based on recommendations [19].

The study was conducted in accordance with the ethical principles described in the

Declaration of Helsinki and was approved by the local ethics committees. Informed consent was obtained from the parents of each newborn.

Serum measurements

The maternal TSH, free triiodothyronine (FT_3), and free thyroxine (FT_4) levels were measured, and the TRAb status was assessed in the third trimester of pregnancy. The umbilical cord was doubly clamped immediately after delivery, and arterial blood was drawn for measurement of the pH, serum levels of TSH, FT_3, FT_4, and NT-proBNP, and the concentrations of TRAb and thyroid-stimulating antibody (TSAb).

The serum TSH, FT_3, and FT_4 levels were assayed using a Roche ECLusys kit (Roche, Basel, Switzerland). The reference ranges in the third trimester were as follows: TSH (mU/L), 0.41−4.01; FT_3 (pg/mL), 2.00−4.90; and FT_4 (ng/dL), 0.82−1.63. The plasma NT-proBNP levels were measured using an Elecsys2010 analyzer with a chemiluminescent immunoassay kit (Roche Diagnostics GmbH, Mannheim, Germany). TRAb (normal range, 0%-15%) and TSAb (normal range, <180%) were measured by a commercially available kit (TRAb-CT RIA kit; Cosmic Corporation, Tokyo, Japan; TSAb assay kit; Yamasa Corporation, Tokyo, Japan). Venous blood samples were collected from each neonate on Days 5, 10, and 30 postpartum

for a re-assay of the serum TSH, FT_3, FT_4, and NT-proBNP levels. The reference ranges of cord blood were as follows: TSH (mU/L), 3.0−30.6; FT_3 (pg/mL), 1.3−2.4; and FT_4 (ng/dL), 1.0−1.7. The reference ranges for 5-day-old neonates were as follows: TSH, 0.4–6.0; FT_3, 2.2–5.0; and FT_4, 1.6–3.2. The reference ranges for 7- to 30-day-old neonates were as follows: TSH, 0.5–4.6; FT_3, 2.7–.4.6; and FT_4, 1.8–2.9 [20]. The reference values of NT-proBNP (mean ± standard deviation) were 818 ± 546 pg/mL on postnatal day 0 (cord blood), 1731 ± 1236 pg/mL on postnatal days 4–8, and 215 ± 169 pg/mL on postnatal days 9–365 [21]. Hyperthyroidism was defined as either TSH below the lower limit of the reference range or undetectable serum TSH levels, and FT_4 above the upper normal range in cord blood and at 5 and 7-30 days of postnatal life. Subclinical hyperthyroidism was defined as either TSH below the lower limit of the reference range or undetectable TSH levels, and normal serum FT_4 and FT_3 levels. Hypothyroidism was defined as TSH above the upper normal range and FT_4 below the lower limit of the reference range at each point of postnatal life. Subclinical hypothyroidism was defined as TSH above the upper normal range levels with normal serum FT_4 and FT_3 levels. Central hypothyroidism was defined as reduced TSH levels with low serum FT_4 levels, as follows: TSH concentration <20 mU/L in combination with FT_4 concentration <0.9 ng/dL [22] [23].

Echocardiography

An echocardiographic examination was performed on each neonate at Days 0, 5, 10, and 30 with the Philips HD11XE (Philips Medical Systems, Andover, MA, USA) device with an 8-MHz transducer. Various parameters were measured using cross-sectional echocardiographic images. The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were calculated using the formula of Teichholz et al [24]. The stroke volume (SV [mL] = LVEDV−LVESV), cardiac output (CO [L/min] = SV × HR), and cardiac index (CI [L/min/m^2] = CO/body surface area) were also evaluated. Measurement of the HR and the echocardiographic examinations were performed during natural sleep.

The echocardiographic examinations were performed by one of two pediatric cardiologists (T. I., S. I.). All of the findings from the examinations were recorded and reviewed by another pediatric cardiologist as a second observer who was blinded to the patients' identifiers.

Statistical analyses

The data are presented as the mean and standard deviation or median and interquartile range

(IQR), as appropriate. The baseline characteristics of the two groups were compared by the two-sided Student's *t* test. The Mann-Whitney *U*-test was used if the variables were not normally distributed. The chi-square test and Fisher's exact test were used for the qualitative categorical analysis. An analysis of variance (ANOVA) for repeated measures was used to evaluate the differences between the groups and changes over time. When a significant difference was indicated by an ANOVA, the specific source of the difference was identified using either the Mann-Whitney *U*-test or a paired *t*-test, with Bonferroni's correction. A p-value of less than 0.05 was considered to be statistically significant.

Results

During the study period, 86 pregnant women with Graves' disease were seen. Newborns with congenital heart disease (n=3) and hemodynamically significant patent ductus arteriosus (n=3) were excluded. Thus, a total of 80 neonates born to mothers with GD were included in the final analysis. There were 36 neonates born to mothers positive for TRAb and 44 born to mother negative for TRAb. The average gestational age at which the maternal TRAb was evaluated was 32.3 ± 3.4 weeks. The baseline characteristics and laboratory data of all of the mothers and newborns are shown in **Table 1**. The mothers positive for TRAb had significantly higher TRAb, FT_3 (p=0.033), and FT_4 (p=0.027) levels and lower TSH (p=0.001) levels than those negative for TRAb, although these values were within the normal range. The rate of receiving anti-thyroid drug (ATD) in TRAb-positive mothers during pregnancy was significantly higher than in TRAb-negative mothers. In addition, the median prepartum doses of ATD (propylthiouracil) in TRAb-positive mothers (n=16) was 150mg/day (IQR 175mg/day). These doses were significantly higher than those in TRAb-negative mothers (n=10: median, 50mg/day; IQR 75mg/day, p=0.001). The cord blood TRAb and TSAb concentrations were significantly higher in TRAb-positive newborns than in TRAb-negative newborns (p<0.001 and p=0.020, respectively).

Table 2 shows the changes in the thyroid function in both groups after birth. At Day 5, the FT_4 levels in the TRAb-positive newborns were significantly higher than those in the TRAb-negative newborns ($p<0.05$). At Day 10, the TRAb-positive newborns had significantly higher FT_3 ($p<0.05$) and FT_4 ($p<0.01$) levels and lower TSH ($p<0.05$) levels than the TRAb-negative newborns, although these values were within the normal range. During the study period, 4 newborns (11.1%) in the TRAb-positive group required treatment with ATD for overt neonatal hyperthyroidism. Eight newborns (22.2%) in the TRAb-positive group were diagnosed with subclinical hyperthyroidism based on findings of laboratory tests in the absence of any clinical symptoms. One neonate in the TRAb-positive group had subclinical hypothyroidism at birth, but there were no symptoms, so no treatment was required. All of the remaining newborns had a normal thyroid function in utero based on the findings in their cord blood at delivery. Detailed information regarding the 12 overt or subclinical hyperthyroid newborns is provided in **Table 3**. None of the newborns in the TRAb-positive group had hypothyroidism or central hypothyroidism.

Three neonates in the TRAb-negative group, whose mothers received ATD until delivery, had subclinical hypothyroidism at Day 5, but there were no symptoms, so no treatment was required. None of the newborns in the TRAb-negative group were diagnosed

with hyper- or hypothyroidism. None of the neonates developed clinical symptoms of hyperthyroidism over the first month.

Table 4 summarizes the changes in the hemodynamic parameters after birth in both groups. The HR and CI at Day 5 were higher in TRAb-positive newborns than in TRAb-negative newborns (both $p<0.05$). At Day 10, the HR ($p<0.05$), SV ($p<0.05$), CO ($p<0.05$), and CI ($p<0.01$) were significantly higher in the TRAb-positive newborns than in the TRAb-negative newborns.

The NT-proBNP levels at Days 5 and 10 were significantly higher in the TRAb-positive newborns (Day 5: median, 752 pg/mL; IQR, 780 pg/mL, $p=0.034$ and Day 10: median, 789 pg/mL; IQR, 713 pg/mL, $p=0.002$) than in the TRAb-negative newborns (Day 5: median, 563 pg/mL; IQR, 297 pg/mL and Day 10: median, 552 pg/mL; IQR, 384 pg/mL). The median NT-proBNP levels in the TRAb-positive newborns at Days 0 and 30 were 346 (IQR 470) pg/mL and 411 (IQR 491) pg/mL, respectively. The median NT-proBNP levels in the TRAb-negative newborns at Days 0 and 30 were 252 (IQR 347) pg/mL and 396 (IQR 301) pg/mL, respectively. There were no significant differences in those levels between the two groups. In addition, the median NT-proBNP levels significantly increased over the first 10 days in the TRAb-positive newborns, while the NT-proBNP levels peaked on Day 5 in the

TRAb-negative newborns (**Figure**).

Table 5 summarizes the changes in the thyroid function and NT-proBNP levels after birth in the TRAb-positive newborns without thyroid dysfunction and with hyperthyroidism. At Day 0, the TSH level in the newborns with hyperthyroidism was significantly lower than those in the newborns without thyroid dysfunction ($p<0.05$). At Day 5, the newborns with hyperthyroidism had significantly lower TSH ($p<0.05$) and higher FT_3 ($p<0.01$) and FT_4 ($p<0.01$) levels than the newborns without thyroid dysfunction. At Day 10, the newborns with hyperthyroidism had significantly lower TSH ($p<0.05$) and higher FT_4 ($p<0.01$) and NT-proBNP ($p<0.01$) levels than the newborns without thyroid dysfunction.

Discussion

This is the first report concerning the hemodynamic changes in neonates born to mothers with GD. The present study showed that the neonates born to GD mothers positive for TRAb had significantly higher CO, CI, and NT-proBNP levels from postnatal days 5 to 10 than those born to GD mothers negative for TRAb.

In the present study, the FT_4 levels at Day 5 in newborns positive for TRAb were significantly higher than those in newborns negative for TRAb. Furthermore, the newborns positive for TRAb had significantly higher FT_3 and FT_4 levels and lower TSH values at Day 10 than did the newborns negative for TRAb. This difference in thyroid function parameters between the two groups was most marked at Day 10, possibly owing to the balance of maternal TRAb and ATD. Neonates born to GD mothers treated with ATD may be hyperthyroid until approximately 7 to 10 days after birth, while they can be euthyroid or even hypothyroid at birth [25]. In the current study, the rate of mothers who received ATD in the TRAb-positive group was significantly higher than that in TRAb-negative group. These results indicated the greater thyroid function in TRAb-positive newborns from postnatal days 5 to 10.

Our study showed that the HR, SV, CO, and CI as well as the FT_4 levels at Day 10 were

significantly higher in the TRAb-positive newborns than in the TRAb-negative newborns. The NT-proBNP levels at Day 10 in the TRAb-positive newborns were also significantly higher than those in the TRAb-negative newborns. Of note, the TRAb-positive newborns with hyperthyroidism had significantly higher NT-proBNP levels at Day 10 than the TRAb-positive newborns without thyroid dysfunction. Thyroid hormone levels increase the blood volume and CO [26-28]. In addition, a combination of reduced systemic vascular resistance and increased venous return, blood volume, myocardial contractility, and oxygen consumption leads to a reduced functional cardiac reserve and decreased exercise capacity because of an inadequate increase in CO [29]. NT-proBNP, which is produced in ventricular cardiomyocytes and secreted in response to volume expansion or pressure overload, is a useful tool for both diagnosing and monitoring cardiac insufficiency and heart failure [30-32]. Clinical evidence has shown that the serum levels of NT-proBNP are strongly affected by the thyroid function; the higher the thyroid function, the higher the NT-proBNP level [33]. Kohno et al. suggested that a potential mechanism for this situation is the influence of secondary hemodynamic changes accompanied by hyperthyroidism on the release of BNP [34]. The results in this study suggested that the elevation of the NT-proBNP levels in TRAb-positive patients was caused by an increased CO, which resulted from an elevated thyroid function.

The plasma NT-proBNP levels in healthy newborns are highest on Day 1. After this marked increase, the NT-proBNP levels rapidly decrease and become stable at the third day of life [21, 35]. However, in our study, the NT-proBNP levels in the TRAb-positive newborns significantly increased over the first 10 days after birth. This finding suggests that these hemodynamic changes are associated with elevated thyroid hormone levels. In the present study, a relatively large number of newborns positive for TRAb were diagnosed with subclinical hyperthyroidism. However, the newborns positive for TRAb had significantly higher CO, CI, and NT-proBNP values than those negative for TRAb from Days 5 to 10. Subclinical hyperthyroidism is associated with an increased HR and left ventricular mass with marginal concentric remodeling and impaired ventricular relaxation [36]. Previous studies have also shown that patients with subclinical hyperthyroidism had significantly higher CO and serum NT-proBNP values than controls or the same patients after treatment [27, 33, 37]. The findings of the present study are compatible with these previous results. Our study suggests that neonates born to GD mothers with a high titer of TRAb are at risk of cardiac complications associated with neonatal Graves' hyperthyroidism, such as high-output heart failure, during the first 10 days after birth.

There are several limitations in the present study, such as the small sample size, with a

small number of newborns having overt hyperthyroidism. In addition, this study did not have a normal control group, which precludes the comparison of hemodynamics between neonates born to mothers with and without GD. However, neonates born to mother negative for TRAb and without ATD treatment might constitute a control group. Future studies with larger populations and a control group may help clarify the hemodynamics in neonates born to mothers with GD in greater detail.

In conclusion, the hemodynamic changes in neonates born to mothers with GD who are positive for TRAb result in significantly higher CO, CI, and NT-proBNP values from postnatal days 5 to 10 than those born to GD mothers who are negative for TRAb. Therefore, physicians should carefully monitor the signs and symptoms related to cardiac complications to help prevent high-output heart failure associated with neonatal GD, especially during the first 10 days after birth.

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Figure Legends

Figure. Box plots showing the distribution of NT-proBNP in both groups at Days 0 (cord blood), 5, 10, and 30. The upper boundary of the box represents the 75th percentile, and the lower boundary of the box represents the 25th percentile. The line through each box represents the median value in each group.

Figure

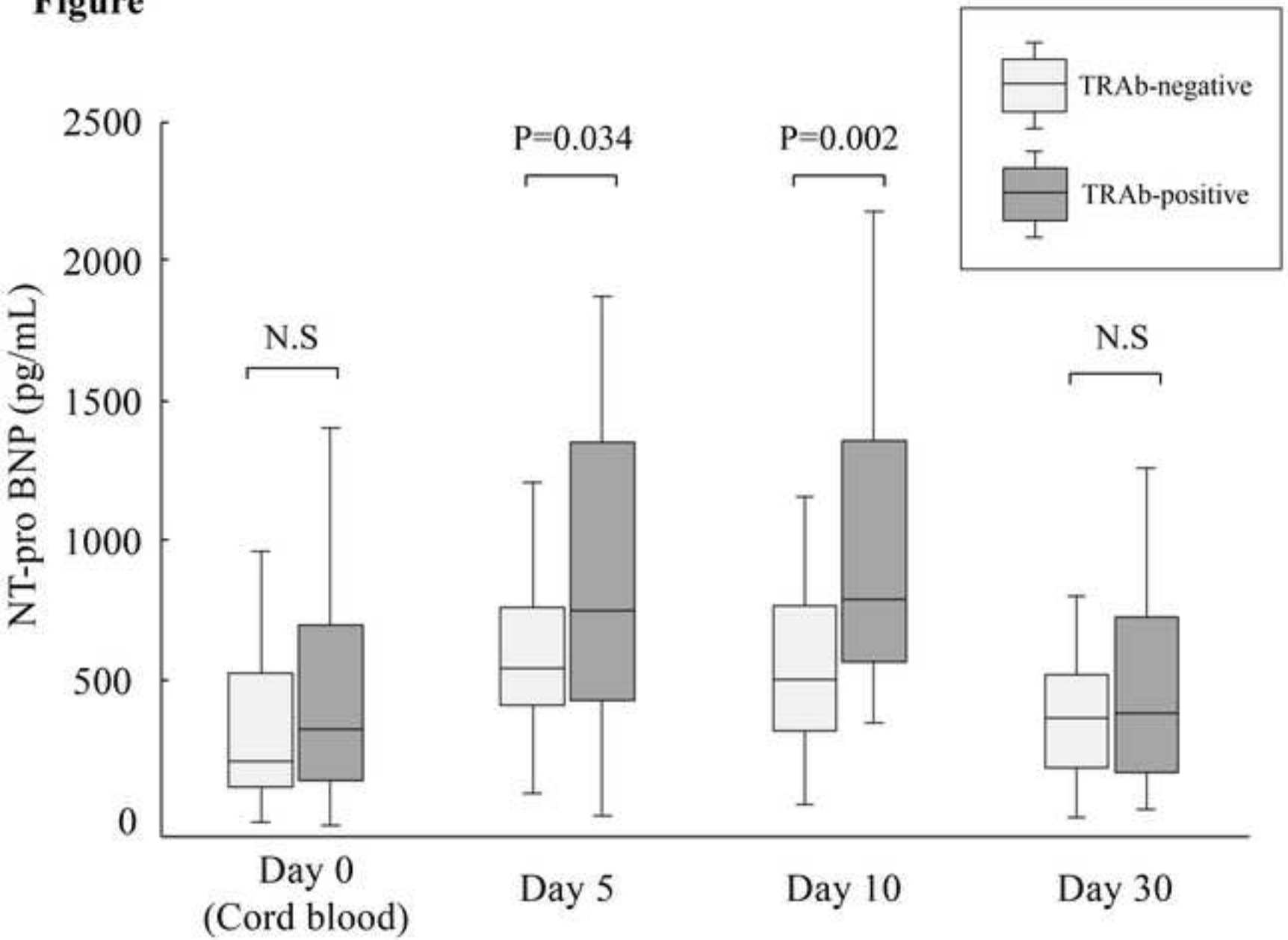

Table 1. The clinical and biological characteristics of the mothers and their newborns

	TRAb-negative (n=44)	TRAb-positive (n=36)	P value
Maternal characteristics			
Age (years)	33.5 ± 5.4	31.3 ± 5.4	0.069
Maternal TRAb (%)	5.9* (11.6)	30.1* (18.8)	<0.001
Maternal TSH (mU/L)	1.20* (1.15)	0.44* (0.62)	0.001
Maternal FT_3 (pg/mL)	2.0* (0.6)	2.5* (1.0)	0.033
Maternal FT_4 (ng/dL)	1.0* (0.2)	1.3* (0.6)	0.007
Treatment before pregnancy			
Thyroidectomy	1 (2.3%)	4 (11.1%)	0.169
Radioiodine	0 (0.0%)	4 (11.1%)	0.037
ATD	11 (25.9%)	20 (55.6%)	0.005
Treatment during pregnancy			
No treatment	28 (63.6%)	16 (44.4%)	0.086
Methimazole	1 (2.3%)	3 (8.3%)	0.322
Propylthiouracil	9 (20.5%)	13 (36.1%)	0.138
Levothyroxine	8 (18.2%)	9 (25.0%)	0.585
Maternal ATD during pregnancy			
1st trimester	13 (29.5%)	20 (55.6%)	0.019
2nd trimester	11 (25.0%)	16 (44.4%)	0.067
3rd trimester	10 (22.7%)	16 (44.4%)	0.039
Newborn characteristics			
Male:Female	19:25	17:19	0.718
Gestational age (weeks)	39.1 ± 1.3	39.2 ± 1.4	0.701
Birth weight (grams)	2901 ± 337	2888 ± 366	0.864
Apgar score at 1 min	8.2 ± 1.2	8.3 ± 1.3	0.732
Apgar score at 5 min	9.1 ± 0.8	9.0 ± 1.2	0.752
Cord blood pH	7.279 ± 0.091	7.300 ± 0.126	0.391
Cord blood TRAb (%)	4.0* (10.7)	26.0* (17.1)	<0.001
Cord blood TSAb (%)	111* (44)	227* (163)	0.020

Values are expressed as the mean ± standard deviation.

* Values are are expressed as the median (interquartile range).

A mother may have received more than one treatment.

ATD, anti-thyroid drug (propylthiouracil or methimazole); TSH, thyroid-stimulating hormone; TRAb, TSH-receptor antibody; FT_3, free triiodithyronine; FT_4, free thyroxine; TSAb, thyroid-stimulating antibody

Table 2. Changes in the thyroid function after birth in both groups

	Day 0 (Cord blood)	Day 5	Day 10	Day 30
TSH (mU/L)				
TRAb-negative	9.18* (4.23)	5.01* (5.55)	4.25* (1.40)	3.84* (2.99)
TRAb-positive	5.31* (5.42)	2.98* (3.56)	2.40* (1.05)$^{\#}$	2.49* (1.01)
FT_3 (pg/mL)				
TRAb-negative	1.4 ± 0.2	3.6 ± 0.7	3.9 ± 0.6	4.2 ± 0.3
TRAb-positive	1.4 ± 0.2	4.0 ± 0.8	4.3 ± 0.5$^{\#}$	4.2 ± 0.6
FT_4 (ng/dL)				
TRAb-negative	1.2 ± 0.1	2.3 ± 0.4	1.8 ± 0.2	1.5 ± 0.2
TRAb-positive	1.1 ± 0.3	2.6 ± 0.4$^{\#}$	2.1 ± 0.4$^{\#\#}$	1.5 ± 0.2

Values are expressed as the mean ± standard deviation.

* Values are are expressed as the median (interquartile range).

$^{\#}$ P < .05; $^{\#\#}$ P < .01 TRAb-negative versus TRAb-positive.

TSH, thyroid-stimulating hormone; FT_3, free triiodothyronine; FT_4, free thyroxine

Table 3. TRAb, TSAb and the thyroid function after birth in newborns with overt or subclinical hyperthyroidism

	Day 0 (Cord blood)					Day 5			Day 10		
	TRAb (%)	TSAb (%)	TSH (mU/L)	FT_3 (pg/mL)	FT_4 (ng/dL)	TSH (mU/L)	FT_3 (pg/mL)	FT_4 (ng/dL)	TSH (mU/L)	FT_3 (pg/mL)	FT_4 (ng/dL)
Overt hyperthyroidism											
Case 1	49.9	434	0.97	0.8	0.8	1.98	3.0	1.9	0.48	4.4	3.0
Case 2	52.9	552	0.82	1.3	1.4	0.18	4.2	2.9	0.08	5.5	3.4
Case 3	76.2	1139	0.01	2.0	1.8	0.34	5.5	4.3	0.44	5.6	3.1
Case 4	91.4	3917	1.64	1.7	1.0	0.17	9.8	7.8	0.02	5.2	2.5
Subclinical hyperthyroidism											
Case 5	37.1	322	2.46	1.6	0.9	6.88	4.4	3.0	2.36	3.5	1.9
Case 6	37.2	441	2.92	2.0	1.5	5.64	4.8	3.1	3.38	4.1	2.8
Case 7	40.5	346	2.02	1.9	1.7	1.24	4.5	3.2	4.11	3.2	2.4
Case 8	37.0	323	1.91	1.8	1.3	6.33	3.9	2.8	2.99	4.4	2.5
Case 9	47.7	305	3.09	2.1	1.7	0.53	5.0	2.9	0.49	4.5	2.9
Case 10	48.0	446	3.21	1.1	1.2	1.29	4.6	2.9	0.48	4.2	2.9
Case 11	42.0	378	2.14	1.4	1.2	0.39	4.0	3.1	0.44	4.6	2.6
Case 12	37.2	311	1.78	2.0	1.6	4.46	3.9	3.0	3.54	3.3	2.7

TRAb, TSH-receptor antibody; TSH, thyroid-stimulating hormone; FT_3, free triiodithyronine; FT_4, free thyroxine; TSAb, thyroid-stimulating antibody

Table 4. Changes in the hemodynamic parameters after birth in both groups

	Day 0	Day 5	Day 10	Day 30
HR (bpm)				
TRAb-negative	142 ± 8.4	132 ± 8.0	126 ± 8.2	114 ± 10.0
TRAb-positive	143 ± 8.9	137 ± 6.7#	135 ± 10.7#	119 ± 15.4
SV (mL)				
TRAb-negative	5.8 ± 1.1	5.7 ± 0.9	6.3 ± 0.5	6.7 ± 0.8
TRAb-positive	5.3 ± 1.2	6.4 ± 1.2	7.1 ± 1.2#	6.9 ± 1.3
CO (mL/min)				
TRAb-negative	812 ± 194	758 ± 133	739 ± 115	722 ± 47
TRAb-positive	802 ± 155	878 ± 210	890 ± 161#	790 ± 129
CI (L/min/m^2)				
TRAb-negative	4.1 ± 0.9	3.9 ± 0.7	3.8 ± 0.6	3.7 ± 0.4
TRAb-positive	4.0 ± 1.1	4.6 ± 1.0#	4.7 ± 0.9##	4.1 ± 0.8

Values are expressed as the mean ± standard deviation.

#P < .05; ##P < .01 TRAb-negative versus TRAb-positive.

HR, heart rate; SV, stroke volume; CO, cardiac output; CI, cardiac index

Table 5. Changes in the thyroid function and NT-proBNP levels after birth in the TRAb-positive newborns without thyroid dysfunction and with hyperthyroidism

	Day 0 (Cord blood)	Day 5	Day 10	Day 30
TSH (mU/L)				
without thyroid dysfunction	10.50* (18.44)	5.69* (3.83)	2.76* (1.83)	3.01* (1.54)
hyperthyroidism	1.97* (1.10)#	1.27* (4.38)#	0.49* (2.65)#	1.86* (1.26)
FT_3 (pg/mL)				
without thyroid dysfunction	1.3 ± 0.5	3.6 ± 0.4	4.2 ± 0.5	4.3 ± 0.6
hyperthyroidism	1.6 ± 0.6	4.8 ± 1.7##	4.4 ± 0.8	3.9 ± 0.6
FT_4 (ng/dL)				
without thyroid dysfunction	1.1 ± 0.5	2.3 ± 0.5	1.8 ± 0.3	1.5 ± 0.2
hyperthyroidism	1.3 ± 0.4	3.4 ± 1.5##	2.7 ± 0.4##	1.4 ± 0.3
NT-proBNP (pg/mL)				
without thyroid dysfunction	372* (609)	686* (949)	582* (780)	348* (458)
hyperthyroidism	293* (377)	794* (555)	1030* (913)#	588* (478)

Values are expressed as the mean ± standard deviation.

* Values are are expressed as the median (interquartile range).

# $P < .05$; ## $P < .01$ without thyroid dysfunction versus hyperthyroidism.

TSH, thyroid-stimulating hormone; FT_3, free triiodothyronine; FT_4, free thyroxine; NT-proBNP, N-terminal-pro-B-type natriuretic peptide