Risk factors of hypothyroxinemia in premature infants

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Abstract

Background: Hypothyroxinemia is defined by low levels of thyroxine (T4) despite low or normal levels of thyroid-stimulating hormone (TSH). This study aimed to evaluate the risk factors associated with transient hypothyroxinemia (THOP) in premature newborn.

Method: This is a single center, retrospective, case-control study. Premature newborns, between 24-34 weeks of gestation, hospitalised between January 2014-December 2019 in our Newborn Intensive Care Unit (NICU) were analyzed through their medical records. Thyroid function tests were routinely performed between the 10th and 20th days of postnatal life and were evaluated according to the gestational age references. Thirty six risk factors (prenatal and postnatal parameters, medical treatments, clinical diagnoses and applications in NICU) were searched in the patient group with THOP (n=71) and the control group with euthyroid prematures (n=73). The risk factors for THOP were identified by univariate analysis, followed by multivariate analysis.

Results: Mean gestational ages of the study and the control groups were 29.7 ± 2.48 and 30.5 ± 2.30 weeks, respectively (p = 0.606). The birth weight, small for gestational age (SGA), intraventricular hemorrhage (IVH), congenital heart disease (CHD) were found to be the risk factors for THOP in the univariate analysis and CHD (p=0.033, odds ratio [OR]:3.7, 95% confidence interval [CI]: 1.1-12.3), BW (p=0.012, OR:0.998, 95% CI: 0.9-1.01) and SGA (p=0.006, OR:5.3, 95% CI: 1.6-17.71) were found to be an independent risk factor for THOP as a result of the multivariate analysis.

Conclusıons: Although some treatment practices might have had direct effects on pituitary–thyroid axis, associated with the severity of the newborn clinical conditions, non of them was found to be a risk factor for THOP. However, preterm babies with CHD and SGA could have more risk for THOP.

1. Background

Transient hypothyroxinemia of prematurity (THOP) is defined by low levels of thyroxine (T4) despite low or normal levels of thyroid-stimulating hormone (TSH)(1). Hypothyroxinemia is observed in around 50 % of premature newborns and its risk increases as the gestational week decreases (2,3). Serum T4 and free T4 (FT4) levels in premature newborns vary according to gestational age in the first days of life. T4 and FT4 concentrations decline to the lowest level between ten and fourteenth days after birth. This situation is more severe with low gestational week and birth weight (BW) (4). In term infants (37–42 weeks' gestation) serum T4 levels characteristically increase in the first week of life whereas in infants born prematurely, and especially those below 30 weeks' gestation, may decrease transiently resulting in a period of hypothyroxinaemia (5,6).

Postpartum TSH and thyroid hormone peaks observed in term newborns are not so evident in preterms. Especially below 30 weeks' gestation, TSH increase is late and weak, while T4 and FT4 levels remain low (7). In premature newborns, physiologicaly low thyroid hormones can be explained by: blunted phsyiolgic hyperthyroidim (correlated with gestational age), increase of thyroid hormone demand (thermogenesis,

cardiac and skeletal muscle functions), deficiencies in iodine metabolism, immaturity of hypothalamo-pituitary-thyroid axis, insufficient response of thyroid gland to TRH, low T4 conversion from T3 and early interruption of maternal T4 transport (8,9). In addition to these factors, thyroid functions may also be suppressed due to medications that are commonly used in premature infants (dopamine, dexamethasone), disorders, such as respiratory distress syndrome, infections, necrotizing enterocolitis, patent ductus arteriosus, malnutrition, chorioamnionitis, as well as iodine deficiency or excess (8,10-12). Thus THOP can be observed due to multiple factors in premature newborns. This study is one of the most important series in the literature which aimed to evaluate the risk factors associated with THOP (4,11,12).

2. Methods

2.1. Participants and datas

This is a single center, retrospective, case-control study. THOP and control groups (euthyroid) of premature newborns who had been matched according to their gestational age were compared. File records of 538 newborns who had been admitted to Istanbul University-Cerrahpaşa Faculty of Medicine Neonatal Intensive Care Unit (NICU) between January 2014-December 2019 were retrospectively analyzed. Recruitment criteria: premature newborns between 24-34 GA, without multiple major congenital anomaly and whose serum thyroid function test were done between the 10th and 20th days of postnatal life. In the 5-year retrospective examination: THOP, euthyroid, primary hypothyroidism and subclinical hypothyroidism were diagnosed in 45.8% (n=83), 47.5% (n=86), 4.9% (n=9) and 1.6% (n=3), respectively. Infants of mothers with maternal hypothyrodism, pregnancy without follow-up was excluded from both THOP and euthyroid groups. Two groups were formed as the patient group (n=71, THOP) and the control group (n=73, euthyroid). The study design was planned as shown in Figure 1.

Thirty six risk factors detected between birth to the time of blood samples collection (prenatal and postnatal parameters, medical treatments, clinical diagnoses and applications in NICU) were compared between the patient group with THOP (n=71) and the control group with euthyroid infants (n=73).

Ethics approval was obtained from Istanbul University-Cerrahpaşa Faculty of Medicine Ethics Committee (reference no: 36423).

2.2. Definitions

Serum free thyroxine (FT4) and TSH levels were measured using commercially available kits (Roche Elecys 2010, USA) by electrochemiluminescence (ECLIA) method. The thyroid hormone levels were assessed based on the weeks' gestational and postnatal age references. In the second postnatal week following intervals were accepted to be the normal range for FT4: 1.45 ± 0.5 ng/dl for 23-27 week, 1.65 ± 0.4 ng/dl for 28-30 week, 1.98 ± 0.4 ng/dl for 31-34 week and the normal range for serum TSH: 3.9 ± 2.7 mU/L for 23-27 week, 4.9 ± 11.2 mU/L for 28-30 week, 3.8 ± 9.3 mU/L for 31-34 week were taken (1). THOP was defined as a low FT4 (as per the age reference interval) and low or normal TSH (as per the age

reference interval) levels (8). Serum TSH and FT4 measurements were performed between the 10th and 20th days of postnatal life.

Bronchopulmonary dysplasia (BPD) was defined as the ongoing need for oxygen after 28 days (13). Echocardiography evaluation was performed by pediatric cardiologist, patent ductus arteriosus (PDA), and other congenital heart diseases (CHD) were recorded. Premature newborns who received a mechanical ventilation or non-invasive ventilation support longer than 24 hours were considered to have these risk factors. Sepsis was diagnosed with positive blood cultures. Severe intraventricular hemorrhage (IVH) was defined as grade 3 or 4, while the presence of severe retinopathy of prematurity (ROP) was defined as grade 3 and beyond based on the International ROP classification (14,15). Fetal growth restriction (FGR) is defined as the failure of the fetus to achieve its genetically determined growth potential (16). The cases whose weight was below the 10th percentile in antenatal percentile follow-ups were defined as FGR by the perinatology department. Small for gestational age (SGA) is defined by birth weight below the 10th percentile for gestational age (17). Central catheterisation was performed in two ways: umbilical arterial/venous cathether and Peripherally Inserted Central Catheter (PICC).

2.3. Statistical methods

The SPSS v.21 (SPSS Inc., Chicago, IL, USA) software was used for the statistical analyzes. The compatibility of the data with normal distribution was evaluated by the descriptive statistics (mean, standard deviation) and Kolmogorov Smirnov Test. Continuous variables were shown with a median (25th - 75th quarters), and categorical variables with frequency and percentage (%). The Mann-Whitney U test was used to compare the groups in terms of continuous variables. The Chi-squared test and Fisher's exact test were used where appropriate in the analysis of the categorical variables. The variables that constituted significant results in the analyses were assessed through a correction made in the single-variable logistic regression analysis based on age, gender and weight. The results were provided with the Odds Ratio (OR) and 95% confidence intervals. The level of significance was taken as $p<0.05$.

3. Results

Characteristics of the THOP and control groups are presented in Table 1. As expected, the FT4 levels were lower in the THOP than the control group (1.00 ± 0.24 and 1.55 ± 0.28 ng/dl, respectively) ($p <0.001$), while there was no significant difference between the TSH levels (4.76 ± 3.36 and 4.32 ± 2.60 mU/L, respectively) ($p=0.556$). Mean birth weight was lower in the THOP group (1306,52 ± 446,44 g) compared to the control group (1544,93± 498,64 g) ($p<0.001$) (Table 2).

In the THOP group, a total of 15 cases of CHD; 8 cases atrial septal defect (ASD), 3 cases ventricular septal defect (VSD), 1 case transposition of the great arteries (TGA), 1 case coarctation of the aorta (CoA), 1 case atrial septal aneurysm, 1 case mitral valve prolapse were detected. In the control group, 4 patients had ASD and 1 VSD. In THOP group, CHD was statistically significantly higher than control group ($p=0.018$, Table 2).

When 36 risk factors were compared between the THOP patients and the control group in univariate analysis: 5th minute Apgar scores, delivery type, FGR, in vitro fertilization (IVF), maternal smoking, gestational hypertension and diabetes, prenatal betamethasone treatments, central catheterisations, sepsis, pneumothorax, PDA, surfactant replacement therapy, drug history (vancomycin+amikacin, ampicillin+gentamisin, caffeine, dopamine, dobutamine, fentanyl, midazolam, paracetamol, ibuprofen, fluconazole), phototherapy, development of hypoglycemia, BPD and ROP, erythrocyte suspension (ES), thrombocyte suspension (TS) and fresh frozen plasma transfusions, mechanical ventilator and noninvasive ventilation support were not statistically significant (Table 2). BW was lower and incidences of IVH, SGA and CHD were higher in the THOP group ($p<0.05$, Table 2). The risk factors suitable for a multivariate analysis (fetal growth retardation, gestational diabetes, 5th minute Apgar score, BW, SGA, dobutamine, ibuprofen, IVH, bronchopulmonary dysplasia, CHD) ($p<0.200$) were analyzed. The CHD ($p=0.033$, odds ratio [OR]:3.7, 95% confidence interval [CI]: 1.1-12.3), BW ($p=0.012$, OR:0.998, 95% CI: 0.9-1.01) and SGA ($p=0.006$, OR:5.3, 95% CI: 1.6-17.71) were found to be an independent risk factor for THOP as a result of the multivariate analysis ($p<0.05$, Table 2-3). As seen in the table 3, the risk of THOP was found to be increased 3.7 and 5.3 times more in premature infants diagnosed with CHD and SGA, respectively. It was also determined that one houndred gram increase in BW reduces the THOP risk by 20% (Table 3).

4. Discussion

In this study, THOP and control groups of newborns who had been matched according to their gestational age were compared. Low birth weight, SGA and CHD were found to be as independent risk factors. These three risk factors are not affected by the gestational age, the severity of the illness and the medical and clinical treatment practices applied. It is already shown in the literature that the frequency of hypothyroxinemia changes in proportion to gestational age (18).

THOP and SGA

In our study, interestingly although THOP group had similiar gestational age with the control group, had a low birth weight in THOP group. Consequently in this study, incidence of SGA was higher in the THOP group and increased the risk of the THOP 5.3 times, one hundred gram increase in BW reduced the THOP risk by 20%. We speculate that being SGA may result in further deficit in storage and adaptive mechanisms. A recent study by Chunhua et al, supported our results that SGA in preterms may be associated with thyroid dysfunction (19). A comprehensive study by Bagnoli et al showed that similar to our results, preterm SGA neonates had lower FT4 compared to preterm AGAs and TSH levels were similar (20). It is generaly accepted that hypothyroxinemia is usually transient in preterm SGAs and is caused by placental hypoxia and delayed maturation of the thyroid gland (21). In addition, some studies underlined that hypothyroxinemia in preterm SGAs might be attributed to nutritional deficiency and might be reversible with the regulation of nutrition (22,23). Similar to the literature, the results of our study suggested that thyroid function tests should be followed more closely in both preterm and SGA newborns.

THOP and CHD

It is well known that thyroid and cardiac disorders can be associated. Congenital heart diseases (5.5%) are frequently associated with congenital hypothyroidism sugggesting common genetic mechanisms involved in thyroid and heart development (24). The association of CHD and thyroid disorder in Down syndrome, which is a genetic disorder, has been well defined (25). In the recent study of HJ Lee et al., it was found that the coexistence of CHD and transient thyroid disorders is approximately 50% (26). In a study with 76 preterm infants hospitalized in neonatal units, cardiovascular disease was significantly higher in THOP (27). In a comprehensive study by Sadia Malik et al., evaluating the relationship between SGA and CHD, it was found that the risk of being SGA was twice as high as in the control group (28). Decreased birth weight, SGA and CHD may have common pathogenetic mechansims that are associated with THOP. Similarly, in this study, hypothyroxinemia was found with a higher rate in preterms with SGA and CHD. It is well known in the literature that the combination of CHD and SGA increases mortality and morbidity (29). Therefore, close follow-up of thyroid function tests is more important in preterms with CHD and SGA.

THOP and prenatal-postnal conditions

Some studies have shown that in preterms thyroid functions are affected by postpartum drugs and some perinatal conditions. Drugs frequently used in premature infants (dopamine, dexamethasone), respiratory distress syndrome, infections, disorders such as necrotizing enterocolitis, patent ductus arteriosus, malnutrition, chorioamnionitis, iodine deficiency or overload may suppress thyroid functions (11, 30-33). It should be noted that gestational age is inversely correlated with the severity of problems in the prematüre newborns which may be associated with more intense medical and invasive treatments. Thus, it is difficult to evaluate whether a risk factor is the consequence of immaturity or the medical treament. Previous studies reported that surfactant, dopamine, glucocorticoids and erythrocyte transfusion increase the risk of THOP (34-37). Most of these studies evaluating the risk factors for hypothyroxinemia belong to the past years and are studies with a smaller number of cases compared to our study.

The medications are used widely as gestational age decrease and severity of the disorder increase. In a study of very low birth weight newborns, it was shown that the negative effect of dopamine and dobutamine use on thyroid function rapidly resolved after treatment was discontinued (38). There are some studies showing that the suppression of thyroid functions has decreased in parallel with the decrease in RDS severity due to the development of prenatal care and neonatal units, especially the widespread use of antenatal steroids and early surfactant treatment in recent years (11). In a study by Lay et al. In recent years, no relationship was shown between THOP and PDA, IVH, antenatal steroid use, ROP, Apgar scores, and sepsis (39). In different pathologies like respiratory distress syndrome, PDA, sepsis, intracranial hemorrhage and necrotizing enterocolitis, it is claimed that their effects on serum thyroid hormone levels are mediated in part by acute inflammatory cytokines (11). In our study, differently from previous studies RDS, PDA, sepsis, IVH, dopamine, dobutamine and erythrocyte suspension transfusion were not found to be the risk factors for THOP. The reason for these different results in our

study, may be due to less needed treatments and their temporary effects with the widespread use of surfactants and antenatal steroids in recent years and the decrease in the severity of diseases in neonatal units.

In this study, serum TFT results between ten and twenty days of life were evaluated according to the postnatal and gestational age reference values, which were generally accepted in the literature and in the largest study on this subject (1). However, there is no TFT level defined as "low or normal" and there is no consensus on the timing of measurements. The strength of this study is that it is one of the few studies (7, 10, 34-38) evaluating so many parameters affecting thyroid functions in premature newborns. On the other hand our study have some limitations as being it is a single center and retrospective study. A multi center and prospective study could create more meaningful results.

In conclusion increase in premature births, improvement of intensive care conditions and survival of these newborns increase the frequency of THOP. There are different recommendations in different studies regarding the frequency and follow-up of THOP. Preterm babies with CHD and SGA could have more risk for THOP. However, prospective studies with broad participation evaluating the prenatal, natal and postnatal risk factors of THOP are needed.

Abbreviations

THOP, transient hypothyroxinemia of prematüre; BW, birth weight; C/S, caesarean; FGR, fetal growth retardation; SGA, small for gestational age; IVF, in vitro fertilization; GDM, gestational diabetes; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; CHD, congenital heart disease; ROP, premature retinopathy; BPD, bronkopulmonary dysplasia; ES, erirtosit suspension; TS, thrombcyte suspension; FFP, fresh frozen plasma; NIV, non invasive ventilation.

Declarations

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from Istanbul University-Cerrahpaşa Faculty of Medicine Ethics Committee and performed in accordance with the tenets of the Declaration of Helsinki. Written informed consents were obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Authors' contributions

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic Features and Laboratory Findings of THOP Patients and Controls

	THOP Group	Control Group	*P Value*
Participants, n	71	73	
Male gender	41 (58)	34 (47)	0.180
GA (wk)	29.7 ± 2.48 (24-34)	30.5 ± 2.30 (26-34)	0.606
FT4 (ng/dl)	1.00 ± 0.24 (0.31-1.58)	1.55 ± 0.28 (0.97-2.54)	**<0.001**
TSH (mU/L)	4.76 ± 3.36 (0.25-10.64)	4.32 ± 2.60 (0.73-13.3)	0.556

Data are given as numbers and (%), after decimal rounded to the greater side. Other data are given as mean ± standard deviation (min-max). When the THOP group and control group cases were compared, FT4 was lower as expected ($p<0.05$, dark stained).

Abbreviations: THOP, transient hypothyroxinemia of prematüre; GA, gestational age.

Table 2. Comparison of Risk Factors for THOP Between Patients and Controls by Univariate Analysis

Risk factors	THOP Group	Control Group	*P* Value
Participants, (n)	71	73	
BW (g)	1306,52 ± 446	1544,93 ± 498	**<0.001**
Apgar score <7 (5th minute)	34 (48)	24 (33)	**0.066**
Apgar score ≥ 7 (5th minute)	37 (52)	49 (67)	
Delivery type (C/S)	63 (89)	67 (92)	0.537
FGR	19 (27)	12 (16)	**0.132**
SGA	15 (21)	4 (5)	**0.006**
PRENATAL			
Maternal smoking	5 (7)	5 (7)	1.000
IVF	8 (11)	7 (10)	0.955
GDM	6 (4)	13 (14)	**0.134**
Gestational hypertension	20 (28)	21 (29)	1.000
Prenatal betamethasone treatment	47 (66)	48 (66)	1.000
MEDICINE			
Vancomycin+amikacin	9 (13)	5 (7)	0.238
Ampicillin+gentamicin	36 (51)	41 (56)	0.511
Surfactant	39 (55)	34 (46)	0.403
Caffeine	59 (83)	57 (78)	0.582
Dobutamine	8 (11)	3 (4)	**0.106**
Dopamine	17 (24)	13 (18)	0.365
Midazolam	23 (32)	21 (29)	0.637
Fentanyl	4 (6)	2 (3)	0.385
Paracetamol	5 (7)	3 (4)	0.442
Ibuprofen	3 (30)	7 (70)	**0,175**
Fluconazole prophylaxis	34 (48)	32 (44)	0.626
CLINICAL-DIAGNOSIS			
IVH	24 (34)	12 (16)	**0.022**
Pneumothorax	3 (4)	4 (5)	0.726
PDA	11/59 (19)*	6/57 (11)*	0.216
CHD	15/59 (25)*	5/57 (9)*	**0.018**
ROP	3 (4)	1 (1)	0.448
BPD	26 (37)	16 (22)	**0.052**
Hypoglycemia	21 (30)	23 (31)	0.802
Sepsis	7 (10)	9 (12)	0.837
TRANSFUSIONS			
ES transfusion	18 (25)	13 (18)	0.271
TS transfusion	5 (7)	5 (7)	0.964
FFP transfusion	23 (32)	19 (26)	0.401
CLINICAL APPLICATIONS			
Phototherapy	66 (93)	68 (93)	0.964
Central catheter	57 (80)	57 (78)	0.905
Ventilator support	31 (43)	28 (38)	0.517
NIV support	48 (68)	54 (74)	0.511

Data are given as numbers and (%), after decimal rounded to the greater side. Values with p <0.2 in univariate analysis are suitable for multivariate analysis (dark stained ones).

*Data are given as cases / total cases with echocardiographic examination.

Abbreviations: THOP, transient hypothyroxinemia of prematüre; BW, birth weight; C/S, caesarean; FGR, fetal growth retardation; SGA, small for gestational age; IVF, in vitro fertilization; GDM, gestational diabetes; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; CHD, congenital heart disease; ROP, premature retinopathy; BPD, bronkopulmonary

dysplasia; ES, erirtosit suspension; TS, thrombcyte suspension; FFP, fresh frozen plasma; NIV, non invasive ventilation.

Table 3. Comparison of Risk Factors for THOP Between Patients and Controls Using Stepwise Multivariate Analysis

Risk factors	*P* Value	OR	95% CI
FGR	0.845	1.111	0.3-3.1
GDM	0.107	0.314	0.1-1.2
Apgar score (5th minute)	0.474	0.896	0.6-1.2
Birth weight	**0.012**	0.998	0.9-1.0
SGA	**0.006**	5.380	1.6-17.7
Dobutamine	0.228	2.429	0.5-10.2
Ibuprofen	0.540	1.610	0. 3-7.3
IVH	0.178	1.829	0. 7-4.3
BPD	0.937	1.040	0.39-2.72
CHD	**0.033**	3.707	1.1-12.3

According to multivariate analysis, birth weight, SGA and detection of CHD were found to be statistically significant ($p<0.05$, dark stained ones).

Abbreviations: FGR, fetal growth retardation; GDM, gestational diabetes; BW, birth weight; SGA, small for gestational age; IVH, intraventricular hemorrhage; BPD, bronkopulmonary dysplasia; CHD, congenital heart disease.

Figures

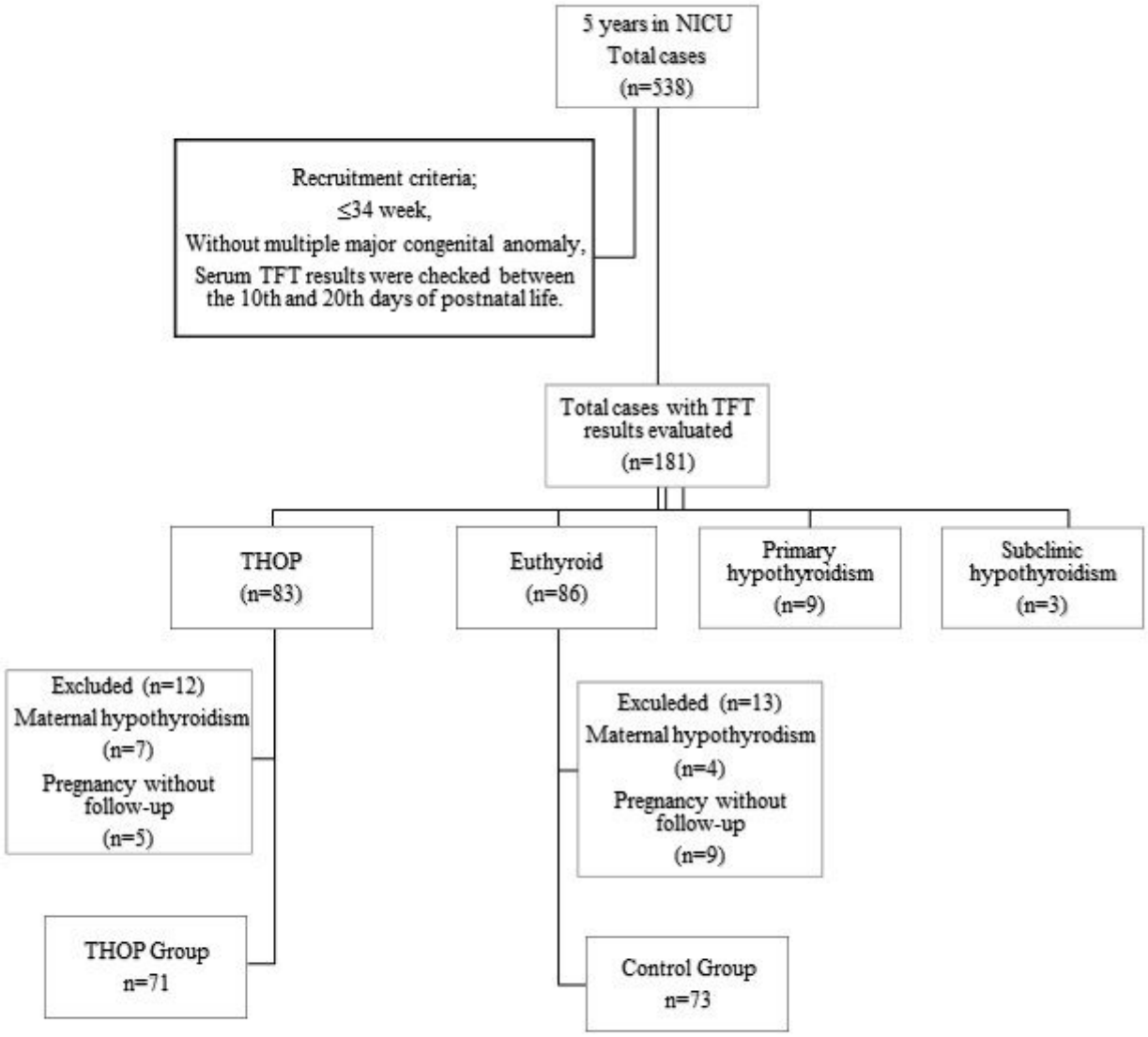

Figure 1

Study design. Abbreviations: TFT, thyroid function test; THOP, transient hypothyroxinemia of prematüre.