

Thyroid hormone Levels in very preterm neonates and extremely preterm

Niveles de hormonas tiroideas en recién nacidos muy prematuros y prematuros extremos

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Abstract

Introduction: The thyroid function of the preterm infant is altered by the relative immaturity of the hypothalamus-pituitary thyroid gland axis, along with other factors such as the incidence of diseases or the use of some drugs. Currently, there is controversy over normal levels of free thyroxine (FT4) in preterm infants. Our objective was to determine the distribution of FT4 and TSH values in newborn younger than 32 weeks or 1500 g of birth weight at 15 days of chronological age, in the neonatology service at Dr. Hernán Henríquez Aravena Hospital, Temuco. **Patients and Method:** Cross-sectional study; the results of FT4 and TSH from a database of 308 newborns, were analyzed, which were categorized into three gestational age ranges, 31-34, 28-30 and 23-27 weeks. It was used Pearson Chi-square for comparisons between categorical variables, and T-Test or ANOVA for categorical-variable ratios. **Results:** Significant differences were observed between the average values of FT4 by gestational age ranges ($p = 0.000$), these were 1.13 ng/dl for the range of 31 to 34 weeks, 1.03 ng/dl for the range of 28 to 30 weeks and 0.92 ng/dl for the range of 23 to 27 weeks; we did not observe significant differences in TSH levels by gestational age categories ($p = 0.663$). **Conclusions:** We established the distribution of FT4 and TSH levels in our population of very preterm and extremely preterm infants, finding differences with previous papers.

Keywords:

Free thyroxine;
Extremely preterm;
Thyroid stimulating hormone

Introduction

Thyroid hormone is essential for the maturation of many tissues, including the brain, as well as for the development of thermogenesis in the neonatal period. The thyroid function of the preterm infant is affected by the relative immaturity of the hypothalamo-pituitary-thyroid axis, along with other factors such as the incidence of diseases or the use of some drugs. An increase in the levels of free thyroxine (FT₄) and thyrotropin (TSH) occurs after birth, similar to that observed in full-term newborns, but at a lesser magnitude in lower gestational age or greater comorbidity. Transient hypothyroxinemia of prematurity, defined as a temporary reduction in FT₄ values without increase of TSH values, can last between six and eight weeks and could explain some degree of delay in the long-term neurodevelopment observed in very low birth weight premature infants¹, however, this condition by itself does not produce a lower IQ or long-term motor alterations, according to the results of a cohort studied until 19 years of age². Hypothyroxinemia usually occurs in ill preterm infants and it is a diagnostic challenge in order to differentiate it from thyroid dysfunction in the critically ill patient. Currently, there is no consensus about normal FT₄ values in preterm infants³⁻⁵, since the abnormality criterion based on the FT₄ value, two standard deviations below the average, seems not to reflect the absence of morbidity in all cases. Previous studies report a prevalence of this disorder in very preterm and extremely preterm infants of 12.2% to 23.5% depending on the cutoff point used⁶⁻⁹.

The benefits of the administration of thyroid hormone in preterm infants are not yet completely clear. In a Cochrane systematic review that analyzed the results of five randomized clinical trials, the authors conclude that there is no significant difference in mortality (RR 0.70 - 95% CI 0.42 to 1.17), risk of cerebral palsy (RR 0.72 - 95% CI 0.28 to 1.84), or abnormal neurological development at six years of age (RR 0.66 - 95% CI 0.22 to 1.99)¹⁰. However, Van Wassenaer (2002) reports significant differences in parameters that assess neurodevelopment at two and five years of age when comparing the results of preterm infants treated with thyroid hormone with plasma FT₄ levels below the 25th percentile (0.78 to 0.97 ng/dl) compared with 75% of higher values (0.97 to 1.63 ng/dl)¹¹. There is also evidence that high levels of thyroid hormones are also associated with adverse events¹². The objective was to determine the distribution of FT₄ and TSH hormone values in newborns younger than 32 weeks or 1,500 g of birth weight at 15 days of chronological age, in the neonatology service of the Dr. Hernán Henríquez Aravena Hospital, Temuco.

Patients and Method

Design

A cross-cutting study was conducted. Clinical variables and results of FT₄ and TSH serum value were collected from an anonymized statistical database of discharge summary from the neonatology service of Dr. Hernán Henríquez Aravena Hospital, Temuco, Chile. Iodine antiseptic solutions are not used in the obstetric and neonatal services of our center, which may alter thyroid hormone concentrations.

Laboratory methods

The laboratory method used for the determination of both levels was chemiluminescent microparticles immunoassay on an Architect analyzer. The samples correspond to venous blood taken at 15 days of chronological age.

Patients

All preterm infants under 32 weeks or less than 1,500 g of birth weight, hospitalized in the Neonatology Service of the Dr. Hernán Henríquez Aravena Hospital in Temuco, between January 1, 2014, and December 31, 2015, were included.

Statistical analysis

The measures of central tendency, dispersion and position were estimated; Pearson's chi-square test was used for associations between categorical variables, and T-Test or ANOVA was used for comparisons between continuous variables. A minimum sample size of 208 subjects was calculated, considering an alpha=0.05, with a level of significance at 95% and an expected proportion in the population of 20%. For the statistical analysis, STATA 13 software was used.

Ethical Considerations

The protocol was approved by the scientific ethics committee of the Universidad Mayor.

Results

The sample consisted of 308 newborns, which were categorized into three groups according to gestational age: 23 to 27 weeks, 28 to 30 weeks and 31 to 34 weeks. 10% (n=31) of the included newborns were connected to mechanical ventilation at 15 days of chronological age, none of the included patients received vasoactive or corticosteroid drugs during the sampling period. Table 1 shows the results of the main clinical variables analyzed. Newborns with a weight lower than p10 were considered small for gestational age according to the Alarcon-Pittaluga growth curves.

Table 1. Of clinical variables between groups categorized by gestational age

	23-27 weeks N = 72	28-30 weeks N = 127	31-34 weeks N = 109	p
Birth weight (g) Mean (std. dev.)	925.5 (224.9)	1237 (273.2)	1484.9 (272.5)	0.000
Surfactant requirement n (%)	48/71 (67.6)	60/126 (47.6)	17/106 (16.03)	0.000
Small for gestational age n (%)	62/72 (86.1)	88/127 (69.2)	41/109 (37.6)	0.000
Abnormal brain ultrasound n (%)	16/69 (23.1)	16/125 (11.8)	11/102 (10.7)	0.06
Abnormal eye fundus n (%)	10/64 (15.6)	1/117 (0.8)	7/78 (9.3)	0.001
Abnormal continuous SpO ₂ n (%)	11/50 (22)	9/98 (9.1)	3/69 (4.3)	0.007

Figure 1 shows the relative distribution of FT₄ and TSH values of the 308 newborns included, both variables have asymmetric distributions. There are significant differences in average values and the distribution of FT₄ values among the groups categorized by gestational age. Figure 2 shows that these differences were not significant in the distribution of TSH values by gestational age. Table 2 shows the position and dispersion measurements of the FT₄ and TSH levels for each category and overall results. In our sample, the 25th percentile of FT₄ was 0.75 ng/dl for the 23 to 27 week group, 0.9 ng/dl for the 28 to 30 week group, and 1 ng/dl for the 31 to 34 week group. The 10th percentile of FT₄ was 0.61 ng/dl for the 23 to 27 week group, 0.81 ng/dl for the 28 to 30 week group, and 0.91 ng/dl for the 31 to 34 week group.

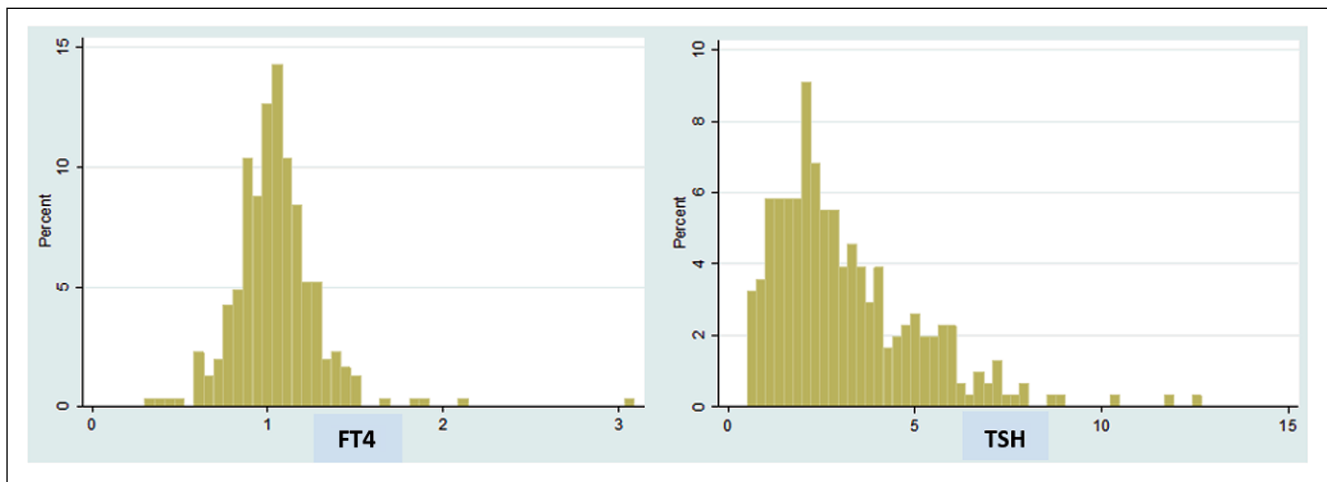


Figure 1. Relative distribution of FT₄ (ng/dl) and TSH (µIU/l) values in 308 newborn younger than 32 weeks or 1500 g of birth weight.

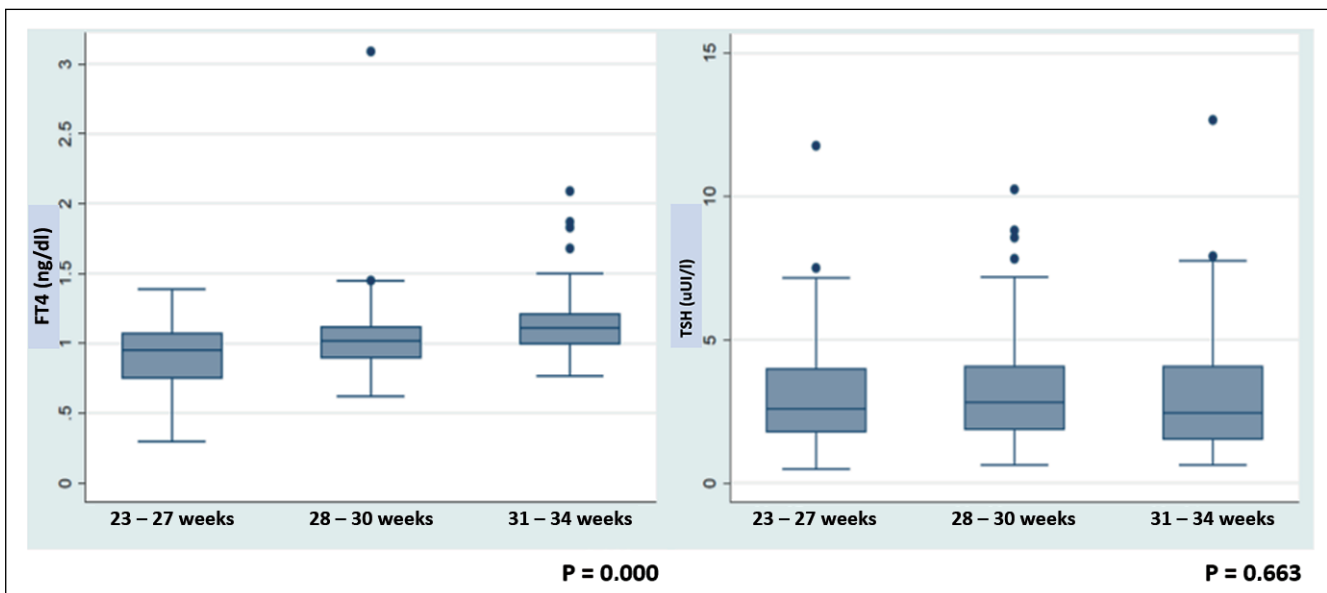


Figure 2. Boxplot, distribution of FT₄ and TSH levels.

Table 2. Distribution of FT4 and TSH values in newborn younger than 32 weeks or 1500g of birth weight

	23 – 27 weeks N = 72		28 – 30 weeks N = 127		31 – 34 weeks N = 109		Total N = 308	
	FT4 (ng/dl)	TSH (μ UI/l)	FT4 (ng/dl)	TSH (μ UI/l)	FT4 (ng/dl)	TSH (μ UI/l)	FT4 (ng/dl)	TSH (μ UI/l)
Mean	0.92	3.11	1.03	3.23	1.13	3.00	1.04	3.12
(std. dev.)	(0.22)	(1.97)	(0.25)	(1.85)	(0.21)	(1.98)	(0.24)	(1.92)
p5	0.51	0.71	0.77	1.13	0.85	0.76	0.7	0.95
p10	0.61	1.04	0.81	1.33	0.91	1.08	0.79	1.16
p25	0.75	1.81	0.9	1.88	1	1.55	0.91	1.74
p50	0.95	2.59	1.02	2.82	1.11	2.46	1.03	2.62
p75	1.07	3.97	1.12	4.08	1.21	4.06	1.15	4.05
p90	1.19	5.92	1.28	5.8	1.41	5.56	1.29	5.8
p95	1.27	7.15	1.32	6.69	1.5	6.72	1.41	6.72

Discussion

The determination of FT4 in very preterm and extremely preterm infants is a standard care in national and global neonatal units, however, there is controversy about what levels are considered normal in this group of newborns. Adams (1995) in a cross-sectional study of 104 preterm infants, with measurements at seven days of age, reports an average FT4 value of 2.4 ng/dl for the 31 to 33 weeks of gestational age range, 2 ng/dl for the 28 to 30 weeks range, and 1.4 for the 25 to 27 weeks range¹³. Williams (2004) in a prospective study of 475 preterm infants, in a measurement of thyroid hormones in cord blood at seven, 15 and 28 days, reports average FT4 values at 15 days of life of 2 ng/dl for the 31 to 34 weeks of gestational age range, 1.6 ng/dl for the 28 to 30 weeks range, and 1.4 for the 23 to 27 weeks range¹⁴. Our results differ from the above-mentioned studies when analyzing the results of FT4 and TSH in 308 preterm infants at 15 days of chronological age, the average values we report are lower for each gestational age range. The reasons for these differences can mainly be explained by the different laboratory tests used in each center and the inclusion criteria for the studied subjects, our study includes a sample of preterm infants under 30 weeks, larger than that of previous publications¹³, our data also show a much smaller dispersion than previously published data. In addition to this, we report position measures such as the 10th percentile or the 25th percentile for three gestational age categories at 15 days of chronological age, which present statistically significant differences ($p = 0.000$), these values could be used as a cut-off point to determine pathological conditions such as transient hypothyroxinemia of prematurity. The average TSH values do not show significant differences between the

three categories of gestational age studied; these results coincide with previous prospective studies¹⁵.

The criteria used to define hypothyroxinemia and, therefore, its prevalence has important variations in previous studies, most of these consider a single cut-off point independent of gestational age. Lee (2015) reports a prevalence of thyroid dysfunction of 12.2% in a sample of 246 newborns under 1,500 g, considering FT4 < 0.7 ng/dl and TSH < 20 mIU/l⁶ as cut-off point; Uchiyama (2015) reports a prevalence of 20% in a sample of 500 newborns under 30 weeks, considering FT4 < 0.8 ng/dl and TSH < 10 mIU/l⁷ as cut-off point; and Lim (2014) reports a prevalence of 23.5% in a sample of 196 newborns under 1,500 g, considering FT4 levels below 0.8 ng/dl and TSH < 5.05 mIU/l (8) as cut-off point⁸. We observed significant differences in the average FT4 values, 25th percentile and 10th percentile when categorizing by gestational age, and other publications also suggest the use of cut-off points according to gestational age ranges. Demirel (2013) reports a prevalence of 15.3% in a sample of 124 newborns under 35 weeks, using FT4 cut-off points categorized by gestational age: < 0.6 ng/dl for infants of 25 to 27 weeks, < 0.8 ng/dl for infants of 28 to 30 weeks and < 1 ng/dl for infants of 31 to 34 weeks⁹, which are consistent with the 10th percentile of our data, except in the 31 to 34 weeks group in which we observed a lower value ($p_{10} = 0.91$ ng/dl).

We identified some limitations of this study, first of all, the study includes patients from a single center, which may limit the ability to generalize the results; second, the study is based on retrospective data stored in statistical databases, therefore, there are variables that could not be analyzed such as triiodothyronine levels, maternal thyroid diseases, to apply severity scales in the included subjects, among others.

In conclusion, we established the distribution of FT4 and TSH levels in our population of very preterm and extremely preterm infants, finding differences with previous studies. We also found significant differences in the average value, 10th and 25th percentile in three gestational age ranges, these results could be used as a cut-off point to determine pathological conditions such as transient hypothyroxinemia of prematurity and use them as a reference for therapeutic targets. We also consider necessary to complement our results with long-term prospective studies in the studied population.

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.

Financial Disclosure

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

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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