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Evaluation of TSH Levels in the Program of Congenital Hypothyroidism Newborn Screening in a Pilot Study of Preterm Newborns in Bogotá, Colombia

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Abstract

Introduction: Preterm infants (<37 weeks of gestation) have low levels of thyroid hormones due to multiple factors. **Objective:** To evaluate levels of thyroid-stimulation hormone (TSH) in the program congenital hypothyroidism (CH) newborn screening in a sample of preterm infants in the city of Bogotá, Colombia. **Methods:** The Secretaría de Salud Distrital screening protocol for CH (blood sample is collected from the umbilical cord in all the newborns) remeasured the serum TSH and heel TSH when preterm infants completed 37 weeks of gestation. **Results:** A total of 59 preterm neonates were rescreened, of which 2 neonates had elevated levels of TSH and 1 neonate had transient hypothyroxinemia. The Kolmogorov-Smirnov 2-sample/bilateral statistical test was used to compare the neonatal TSH levels of preterm and full-term newborns, which do not follow the same distribution. **Conclusion:** In our pilot study, 2 of the rescreened infants presented high levels of TSH and 1 had transient hyperthyrotropinemia, suggesting the need for rescreening of preterm infants. Additionally, a larger study should be performed to determine the screening cutoff values for preterm newborns.

Keywords

hypothyroidism, preterm neonates, full-term neonates, rescreening, TSH

Newborn screening (NBS) is an essential part of the public health system. Due to the remarkable progress in the clinical care of preterm neonates (<37 weeks of gestation), their survival has dramatically improved. In fact, in developed countries, more than 90% of extremely preterm infants (<28 weeks of gestation) survive, showing an increase in the threshold of fetal viability.[1] However, the immaturity of the preterm implies the requirement of redefining the clinical parameters for diagnosing diseases and establishes new margins of normal physiology of the fetus.

In Latin America, a common reason of neonatal screening is for congenital hypothyroidism (CH). Congenital hypothyroidism is the most widely screened disease; nonetheless, there is still debate around standard thyroid-stimulation hormone (TSH) levels, sampling techniques, and population coverage, showing tremendous heterogeneity among countries.[2,3]

In Colombia, the prevalence of CH has been estimated to range from 1:1.886 to 1:3.300.[4,5] Since 2000, CH is the only mandatory screening disease in the neonates,[6,7] and the detection levels of TSH are based on levels of full-term newborn (TSH cutoff for CH detection: $\geq$15 mU/L of TSH).[8]

In the major cities such as Bogotá, District of Colombia, there is almost full coverage for CH neonatal screening and there is also an increasing number of tertiary neonatal intensive care units, implying that neonatal viability has increased, and there can be better medical care for preterm neonates even in developing countries.[9] However, the cutoff for CH detection has not been adapted for preterm neonates since its

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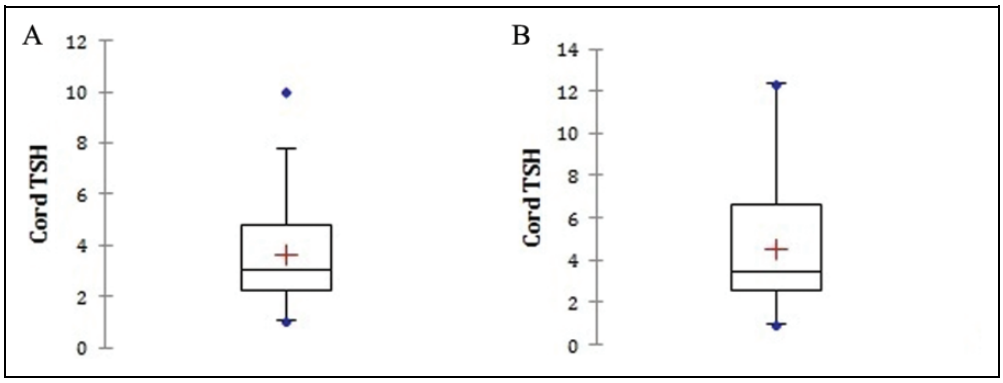

Figure 1. Boxplots of the distribution of cord blood TSH levels. A, Boxplot of cord blood TSH levels distribution in preterm neonates. Mean is 3.64 mU/L; 1 preterm neonate presented a high TSH level of 10.06 mU/L. B, Boxplot of the distribution of cord blood TSH levels in full-term babies. Mean is 4.56 mU/L. TSH indicates thyroid-stimulation hormone.

implementation, and there are no local studies revolving around the best cutoff level for detection in preterm neonates.

The aim of this exploratory study is to reevaluate TSH levels in a group of preterm neonates who were assessed by the government program of CH screening, in order to establish accurate cutoff level for detection and to determine some of the challenges that the screening process faces in the context of preterm neonates.

Materials and Methods

This is an exploratory study based only on 1 registry for Bogotá, Colombia. The objective was to evaluate TSH levels in CH NBSs from a sample of preterm infants assessed by the Secretaría de Salud Distrital (SSD) program.

The SSD NBS program consists of the following strategy:

- A blood sample from the umbilical cord is collected from all the newborns. We use a whole blood level.
- The TSH levels are measured using standard immunoassay system (automatic immunoassay test system AutoDELFIA).[10]
- With a cutoff of $\geq$15 mU/L, the newborns are either classified as having a normal TSH level and discharged from the program or, if a TSH level at or above the cutoff is detected, TSH is measured in peripheral blood sample. If the levels are altered, treatment is prescribed.

In this study, a new blood sample (heel) is collected in the preterm neonates when they reach the corrected 37 weeks of gestational age. This sample is taken as a result of the CH screening process, although TSH levels is also measured in a peripheral blood sample (serum levels) as a part of the routine clinical attention; therefore, the preterm neonate has double sampling of TSH.

We selected a convenience sample of newborns from the SSD NBS program records in the Hospital La Victoria. For all the cases, the procedures for CH screening program, demographic data, and TSH levels were collected. For statistical analysis, we performed descriptive statistics and measures of central tendency with a confidence interval (CI) of 95%. The normality test of hormone level distribution was performed using the Shapiro-Wilk test. In order to assess the homogeneity of the hormone level distribution among the preterm group and the full-term neonates, we used the Kolmogorov-Smirnov test. Statistical analysis was performed using Excel 2011 and XLSTAT 2013.

Results

We collected CH screening information for 118 neonates assessed by the SSD program. The preterm group consisted of 59 infants, 28 females (47.5%) and 31 males (52.5%), with gestational ages between 28 and 36 weeks (mean: 32.8 weeks). The full-term group consisted of 59 full-term neonates, 29 females (49%) and 30 males (51%), with gestational ages more than 37 weeks (mean: 39 weeks). The excluded neonates were those with multiple congenital abnormalities, known chromosomal disorders, and infants of hypothyroid mothers.

Cord whole-blood TSH levels in the preterm group had a mean of 3.64 mU/L (range: 1.06-10.06 mU/L, standard deviation [SD]: 1.93; 95% CI of 3.15-4.13). Cord whole-blood TSH levels in the full-term group had a mean of 4.56 mU/L (range: 1-12.4 mU/L, SD: 2.78; 95% CI 3.85-5.27). There was only 1 outlier in the preterm group, with a value of 10.06 mU/L. During the rescreening, this preterm newborn had a serum TSH level of 12.49 mU/L; however, in 2 subsequent samples (with 1 week between each sample), the TSH levels in plasma were normal, and this patient did not require treatment with levothyroxine, implying that the patient presented a transient hyperthyrotropinemia. The box plots of the distributions of cord TSH levels are shown in Figure 1A and B.

The TSH level distributions of both preterm and full-term neonates followed a nonnormal distribution (Shapiro-Wilk test for neonatal TSH in preterm neonates, $W = 0.918$; P value = .001; $\alpha = .05$. Shapiro-Wilk for full-term neonates, $W = 0.901$; P value = .0001; $\alpha = .05$). Both distributions were similar (Kolmogorov-Smirnov test, $D = 0.203$; P value = .153; $\alpha = 0.05$; Figure 2); however, an estimation of quantiles of the

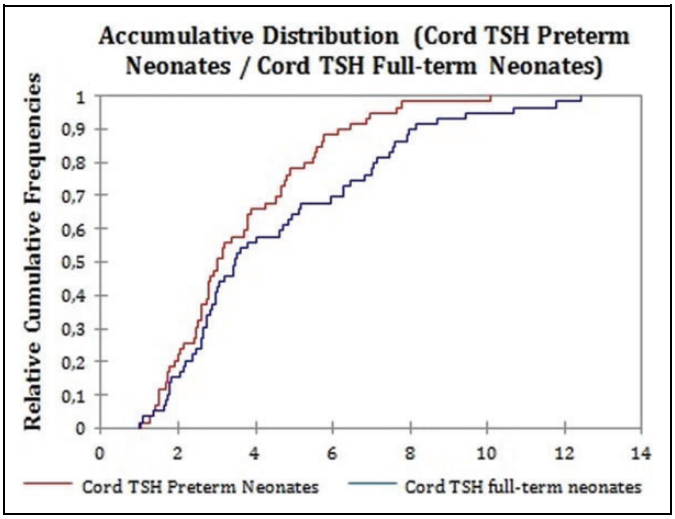

Figure 2. Cumulative distribution of cord blood thyroid-stimulation hormone (TSH) levels in preterm neonates (red) and cord full-term neonates (blue). Both distributions are similar. Kolmogorov-Smirnov test, D = 0.203; *P* value = .153; $\alpha = .05$.

distribution showed that the 85th percentile in the preterm corresponds to 5.6 mU/L whole-blood TSH level (Figure 3A) and 7.5 mU/L whole-blood TSH level in the full-term neonates (Figure 3A and B).

In the preterm group, 2 neonates had elevated levels of TSH once they reached the corrected gestational age of 37 weeks. The first patient was a preterm neonate of 34 weeks of gestational age, with normal umbilical cord TSH levels, who presented 17.32 mU/L TSH serum levels at corrected age of 37 weeks (normal range: 1.36-8.80 mU/L). The second patient was a preterm neonate of 36 weeks of gestational age, with normal umbilical cord TSH levels, who presented 13.67 mU/L TSH serum levels at corrected age of 37 weeks (normal range: 1.36-8.80 mU/L). The first patient began treatment with levothyroxine immediately after the diagnosis was confirmed. Unfortunately, the second patient was lost to the program, and currently we do not know whether she is receiving treatment.

Discussion

Given the metabolic implications of preterm infants (maternal–placental T4 transfer, hypothalamic–pituitary–thyroid immaturity, developmental constraints on the synthesis and peripheral metabolism of iodothyronines, iodine deficiency, and nonthyroidal illness) cause low levels of thyroid hormones,[11] and the more preterm the neonate is, the more immature the fetal thyroid is to produce enough T4 for the high postnatal requirements.[11-13] This alteration in thyroid hormone homeostasis correlates with elevated prenatal morbidity and death rate.[14] Regardless of this physiological situation, in our population, these biological aspects are not taken into account and there is no differentiation in the cutoff levels for preterm and term neonates. Besides, preterm neonates are not rescreened, which can result in the presence of false negatives. Notwithstanding the limitations of this study (exploratory sample), this showed that the populations of both preterm and full-term neonates were homogeneous, which allowed undertaking an appropriate comparison between TSH cord levels. We observed that the levels were lower in preterm newborns than in the full-term newborns; however, an estimation of quantiles of the distribution showed that the 85th percentile in the preterm corresponds to 5.6 mU/L whole-blood TSH level and 7.5 mU/L whole-blood TSH level in the full-term neonates, so the cutoff in the neonatal screening ($\geq$15 mU/L) should be lower for preterm. This is very debatable as there is no consensus for the cutoff in the newborns. For example, the recommended cutoff for investigation of CHT = CH (Congenital Hypothyroidis) in the United Kingdom is a blood spot TSH of 10 mU/L, but in other regional thresholds (Northeast England) it is 6 mU/L.[15,16] It is important to mention that, unlike many countries such as Uruguay and Singapore—which previously performed screenings in umbilical cords but now use dried blood spots—Colombia currently still screens in umbilical cords because the screening program is needed to ensure 100% coverage and because of the socioeconomic difficulties in the Colombian population to bring infants to screenings, since newborns are not in the health centers more than 24 hours after delivery. However, in recent years, Colombian Institute of Health has been working to expand screenings and do them in dried blood spots.

While rescreening, 2 preterm infants had high TSH levels after completing 37 weeks of gestation. The preterm infant who presented with a high cord whole-blood TSH level (10.06 mU/L) had a TSH serum level of 12.49 mU/L in the rescreening, but in the control was standard, so the infant did not require therapy. In the review of literature, there are several reports about the quality of rescreening of preterm newborns around the world: Chung et al[17] studied 105 preterm infants and showed that 31 (29%) had hypothyroxinemia and 13 (12%) had CH. Goissen et al[18] reported 29% as the incidence of transient hypothyroxinemia in preterm infants <32 weeks of gestation and 64% at <28 weeks. Srinivasan et al[15] showed the similarity between incidence of CH in preterm and full-term neonates. Profound abnormalities of thyroid function can occur in preterm babies with transient hypothyroidism, but both categories of hypothyroidism can be detected by a single TSH screening with a relatively low cutoff. However, in the United Kingdom, there is a policy to repeat the sample in preterm; this policy is based on gestational age criteria and includes infants born at less than 32 weeks gestation ($\leq$31 + 6 days) and repeat testing at 28 days postnatal age, counting day of birth as day 0.[16] The challenges inherent in planning any NBS program are many, from deciding which tests will be performed to identifying when and how many (serial) samples should be collected, and if they are preterm, it is even more complicated. Then, too, the delayed development of some metabolic systems in preterm newborns can cause inaccuracy in NBS tests for some conditions. Even life saving infused nutritional support can create confusion in the interpretation of metabolic NBS results, whereby the Clinical and Laboratory Standards Institute

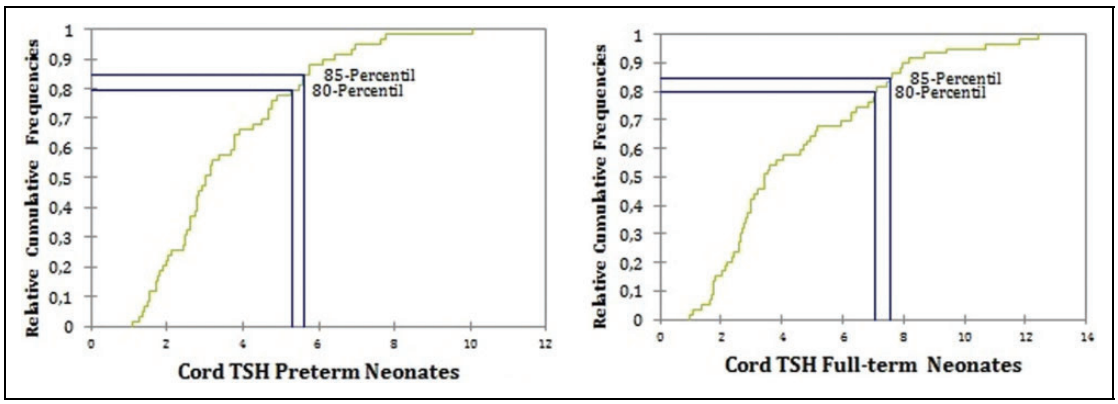

Figure 3. Relative cumulative frequencies of cord blood TSH levels. A, Relative cumulative frequencies of cord blood TSH levels in preterm neonates. Percentile 80: 5.31 mU/L. Percentile 85: 5.61 mU/L. B, Relative cumulative frequencies of cord blood TSH levels in full-term neonates. Percentile 80: 7.06 mU/L. Percentile 85: 7.55 mU/L. TSH indicates thyroid-stimulation hormone.

published a guideline for NBS for preterm, low birth weight, and sick newborns, recommending a first screening upon admission to a sick child birthing unit, again at 48 to 72 hours of life, and once more at discharge or day 28 of life.[19,20] All this indicates the importance of the reappraisal of the preterm population or changing the cutoff for preterm.

This pilot study, regardless of the limitations from the sample size and no follow-up of newborns, achieved showing a difference between the levels of neonatal TSH in preterm and full-term infants. In addition to rescreening of preterm infants, it was observed 1 correlation between serum and heel levels of TSH. Moreover, this study found high levels of TSH in serum of 2 of these infants, in which diseases that could elevate TSH were discarded, given the persistent elevation in TSH required management using levothyroxine, although these patients require monitoring to assess the need for further treatment. However, by not having a sufficiently large sample, there is no correlation possible between screening parameters (sensitivity, specificity, and positive predictive value) and the different sample timing, and further study with a larger population is necessary to become conclusive.

Conclusion

While rescreening, 2 preterm infants had high TSH levels when completing 37 weeks of gestation and 1 preterm infant presented high TSH levels in the rescreening, with subsequent normal controls that never required management. There is a clear difference between the levels of TSH in preterm and full-term infants, which shows that the levels of TSH in preterm are lower, so it is necessary to perform a more robust study that can identify a cutoff for preterm infants. Colombia requires a special protocol for CH NBS in preterm infants.

Declaration of Conflicting Interests

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