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Prevalence of high neonatal thyroid stimulating hormone levels as an indicator of iodine deficiency in the province of La Pampa: An epidemiological analysis

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ABSTRACT

Introduction. Iodine plays a key role in human metabolism, growth, and development. During pregnancy and childhood, the demand for this micronutrient increases notably. Increased neonatal thyroid stimulating hormone (nTSH) levels, defined as nTSH ≥ 5 mIU/L, are a marker of iodine deficiency in a population if its prevalence is higher than 3%.

Objective. To establish the prevalence of nTSH ≥ 5 in La Pampa in the 2021–2022 period, analyze its correlation with different variables, and compare it with data from a historical cohort.

***Population and methods*.** Cross-sectional, descriptive-analytical study in a population of newborn infants born in the 5 health regions of the province of La Pampa in 2021 and 2022.

Results. Of the 5778 assessed newborn infants, 9.6% had nTSH levels ≥ 5 mIU/L. It was reported that 70.4% of these measurements were done after the third day of life. No significant differences were observed in the frequency of high nTSH levels by year of birth, birth weight, or days until sample collection. A higher prevalence was observed among male infants (10.6% versus 8.5%; $p = 0.007$) and term infants (9.8% versus 6.6%; $p = 0.02$). The prevalence of high TSH levels was superior to that observed in the 2001–2002 cohort.

Conclusions. The prevalence of high nTSH levels in La Pampa during 2021 and 2022 was 9.6%, suggesting the presence of mild iodine deficiency in the population of this province, higher that what had been reported 2 decades ago.

Keywords: *thyroid hormones; thyroid stimulating hormone; iodine; neonatal screening; iodine deficiency.*

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INTRODUCTION

Iodine is an essential micronutrient for the synthesis of thyroid hormones which, in turn, regulate human metabolism, growth, and development.[1–3] Nutritional requirements increase significantly during pregnancy and childhood. The fetal nervous system is especially vulnerable because thyroid hormones are crucial for neuronal migration and myelination.[2–4]

Iodine deficiency (ID) has multiples detrimental effects on growth and development. During pregnancy, ID increases the risk of neonatal death, miscarriages, congenital anomalies, intrauterine growth retardation, and neurological problems of varying severity.[1,3–6] Severe ID may cause severe intellectual impairment; even the mild form may trigger neurodevelopmental disorders.[5,7]

Worldwide, the main strategy to prevent ID is the iodization of salt for human consumption. This strategy has been implemented for more than a century and has successfully eradicated endemic cretinism and severe manifestations of ID in most countries.[1,3,8] To maintain its effectiveness, this preventive strategy requires an ongoing effort, including constant monitoring of salt iodization and periodic surveillance of the population's iodine nutritional status.[1,3]

Among other indicators, neonatal thyroid stimulating hormone (nTSH) levels are used to assess a population's iodine nutritional status. nTSH is used in neonatal screening protocols to obtain individual information about thyroid function. In addition, the analysis of the prevalence of nTSH levels ≥ 5 mIU/L (high nTSH levels) helps to establish the presence or absence of ID at the population level.[9–12] According to the bibliography, a prevalence of high nTSH levels of less than 3% of newborn infants suggests an adequate iodine nutritional status in the population.[1]

In the province of La Pampa, a study conducted by our group more than 20 years ago found a prevalence of nTSH levels ≥ 5 mIU/L of 7.65%. This indicates the presence of mild ID in that period.[13]

The objectives of this study were to investigate the prevalence of high nTSH levels in La Pampa and analyze its relationship with different variables, such as sex, gestational age, birth weight, health region, and days of life at the time of measurement. We also sought to compare the prevalence of nTSH levels ≥ 5 mIU/L in our study cohort of 2021–2022 with the results obtained in 2001–2002.

POPULATION AND METHODS

This study was conducted at Establecimiento Asistencial Dr. Lucio Molas (EALM) of Santa Rosa, a public hospital with a coverage area of approximately 150 000 inhabitants. This was a cross-sectional, descriptive-analytical study that included newborn infants born across the 5 health regions of La Pampa between 2021 and 2022. Newborn infants diagnosed with congenital hypothyroidism, those exposed to the use of iodine antiseptics (reported to the laboratory by staff involved in delivery), and measurements performed after 15 days of life were excluded.

Data source

Database of the National Program for the Reinforcement of Newborn Screening (Programa Nacional de Fortalecimiento de la Pesquisa Neonatal, PNPN), spreadsheets of the Department of Laboratory, and Health Information System of La Pampa.

Sampling and detection technique of neonatal thyroid stimulating hormone levels

In 2021 and 2022, nTSH measurements from the provincial public sector were performed centrally by the EALM. Samples were obtained after 48 hours of life or at the time of neonatal discharge, using filter paper. The nTSH analysis was done in accordance with the regulations and using the reagents provided by the PNPN. A semi-automated, ELISA-like quantitative assay by ZenTech was used.

An electrochemiluminescence technique had been used in 2001 and 2002.

Study variables

The following data were obtained from the PNPN: place of origin of the sample, gestational age (GA) in weeks, birth weight (BW) in grams, days of life at the time of the sample collection, and use of iodine disinfectants during delivery. Gestational age was divided into 3 groups: preterm (≤ 36 weeks), term (37–41 weeks), and post-term (≥ 42 weeks).

Data for the variables sex and result of the first nTSH sample were obtained from the other sources.

Statistical analysis

The R statistical software, version 4.2, was used. Categorical variables were described as number and percentage (%), whereas continuous variables were expressed as median (25^{th}–75^{th}

percentiles). The comparison between 2 groups was done using the Mann-Whitney test for continuous variables, while the χ^2 test was used to compare the frequency of nTSH levels ≥ 5 mIU/L between groups of interest. The comparison of the frequency of nTSH levels ≥ 5 mIU/L between the 2001–2002 and the 2021–2022 cohorts was done using a contingency table and the χ^2 test. Differences were considered significant if the *p* value was < 0.05.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki ethical principles. The protection of patient identity was warranted by eliminating personally identifiable information from the database. Confidentiality was maintained by coding and restricting access to the database. The study was approved by the EALM's Research Ethics Committee, and an informed consent waiver was granted (53/2022).

RESULTS

During 2021 and 2022, the PNPN of the province of La Pampa registered a total of 5885 newborn infants. Of these, 96 were excluded because their nTSH measurements were done after the 15 days of life; 3, because they had been diagnosed with congenital hypothyroidism; and 8, because they had been exposed to iodine antiseptics during labor. The final sample included 5778 newborn infants; 50% were female. *Figure 1* shows the flow chart of patient inclusion.

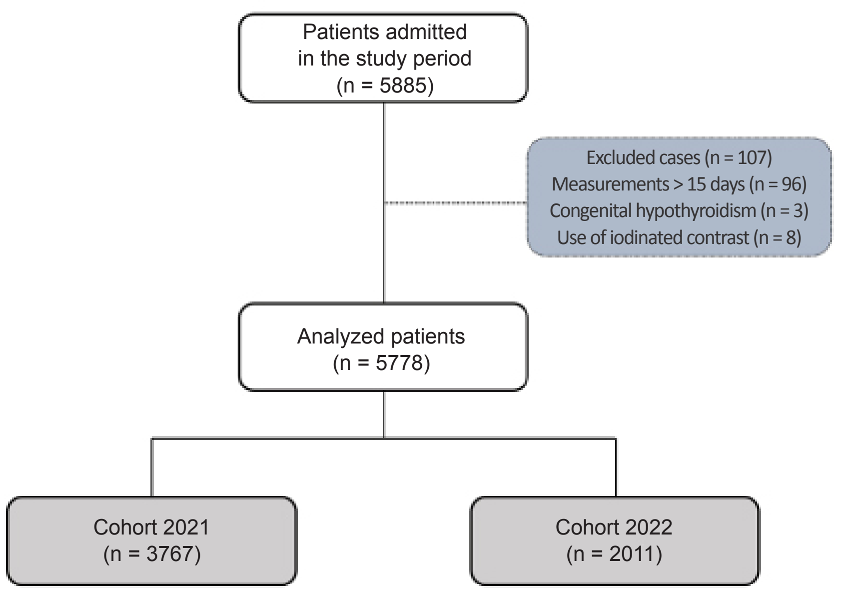
Their median GA was 39 weeks (interquartile range: 38–40). Their median BW was 3330 g (interquartile range: 3000–3650), and 7.5% of newborn infants had a BW of less than 2500 g. In addition, 91.6% of newborn infants had been born at term, while 8.3% had a preterm birth. Most newborn infants had been born in health regions 1 and 2 (region 1: 44.98%, region 2: 43.35%).

nTSH was measured after the third day of life in 70.4% (median time of sample collection: 4 days old [2–6]). The time of sample collection varied depending on them being term or preterm newborn infants (term: 4 days [2–6] versus preterm: 5 days [3–7]; $p < 0.0001$). *Table 1* describes the sample characteristics by year of birth.

In 9.6% of newborn infants, the nTSH level was ≥ 5 mIU/L. No differences were observed in the frequency of nTSH levels ≥ 5 mIU/L by year of birth (9.3% in 2021 versus 9.9% in 2022; $p = 0.46$); it was higher among males (10.6% versus 8.5%; $p = 0.007$) and among term newborns compared to preterm newborns (9.8% versus 6.6%; $p = 0.02$). The frequency of nTSH did not vary by BW, either equal to or greater than 2500 g or less than 2500 g (< 2500 g: 7.4% versus ≥ 2500 g: 9.7%; $p = 0.12$) or the days of life at the time of sample collection (≤ 2 days: 9.9% versus ≥ 3 days: 9.4%, $p = 0.58$).

In relation to health regions, as seen in *Table 2*, the frequency of nTSH levels ≥ 5 mIU/L was remarkably higher in region 2 compared to

Figure 1. Flow chart of included newborn infants. La Pampa, 2021–2022



regions 1, 4, and 3 + 5 (χ^2 test, Bonferroni post-test correction; $p < 0.00001$).

Compared to the 2001–2002 cohort, the prevalence of TSH levels ≥ 5 mIU/L was higher (*Table 3*).

DISCUSSION

By 1999, most of the world's countries, including Latin American nations, had achieved the goal of universal iodization of salt for human consumption. This progress contributed to the control or reduction of ID at the population level.[1,14] The need to monitor this condition has always been part of this successful preventive strategy, but it has become essential in the past decade given the re-emergence of ID in different regions of the world.[1,7,15-18]

A prevalence of nTSH levels ≥ 5 mIU/L below 3% suggests an adequate iodine nutritional status in the population.[1] According to several studies included in a comparative meta-analysis of population ID indicators, nTSH is the most accurate marker for assessing long-term iodine intake.[19] Specifically, nTSH has been shown to be more sensitive in populations with mild to moderate ID and is especially useful as an indicator of iodine intake during pregnancy.[10,11,19] In this study, the prevalence of nTSH levels ≥ 5 mIU/L was 9.6%, suggesting mild ID in the population of La Pampa.

nTSH levels may be affected by several factors, such as dietary iodine intake, maternal thyroid function, and fetal distress, both maternal and neonatal or obstetric. These factors include the use of iodine antiseptics during delivery, preterm birth, low BW, male sex, and days of life at the time of sample collection.[11,20,21]

This study found a higher prevalence of nTSH levels ≥ 5 mIU/L among term newborns than preterm newborns. These findings are consistent with research describing a higher incidence of thyroid dysfunction among preterm newborn infants, especially extremely preterm infants, due to the immaturity of the hypothalamic-pituitary-

Table 1. Characteristics of the sample by year of birth; n = 5778

	Year 2021 (n = 3767)	Year 2022 (n = 2011)	*p* value
Female sex (%)	1884 (50)	1005 (50)	ns*
Gestational age (weeks)	39 (38–40)	39 (38–40)	ns*
Birth weight (grams)	3330 (3010–3650)	3310 (3000-3620)	ns**
Days of life at the time of measurement (days)	4 (2-6)	4 (2-6)	ns**

n: number, ns: not significant.
** χ^2 test.*
*** Mann-Whitney test.*

Table 2. Frequency of high neonatal thyroid stimulating hormone levels by health region

	Health regions (n = 5778)				
	1 (n = 2599)	2 (n = 2505)	3 + 5 (n = 493)	4 (n = 181)	*p* value
nTSH ≥ 5 mIU/L (%)	201 (7.7)	301 (12)	39 (7.9)	11 (6.1)	< 0.00001*

n: number, nTSH ≥ 5 mIU/L: high neonatal thyroid stimulating hormone levels.
** χ^2 test, Bonferroni post-test correction.*

Table 3. Comparative analysis between the 2001–2002 cohort and the 2021–2022 cohort

	2001–2002 cohort n = 2035	2021-2022 cohort n = 5778	*p* value
nTSH ≥ 5 mIU/L	156 (7.66%)	552 (9.56%)	0.011*

n: number, nTSH ≥ 5 mIU/L: high neonatal thyroid stimulating hormone levels.
* χ^2 test.

thyroid axis. As a result, postnatal TSH levels are lower, and even the postnatal TSH peak level may be delayed by days or weeks in preterm newborns compared to term newborns. Another factor that may influence this difference is the use of glucocorticoids, which are used before some preterm deliveries to promote lung maturation and have an inhibitory effect on TSH secretion.[22–24]

In addition, no significant differences were observed in the frequency of nTSH levels ≥ 5 mIU/L between newborn infants with a BW equal to or greater than 2500 g or less than 2500 g. The absence of differences is likely due to the fact that ID in our population is mild, and fetal growth impairment occurs mainly in areas with moderate or severe ID. In this regard, some studies suggested that maternal supplementation with iodine may increase BW compared to the infants born from mothers who did not receive such supplementation.[3]

Consistent with our study, an investigation conducted in Spain described a higher prevalence of nTSH levels ≥ 5 mIU/L in male infants compared to female infants.[21] So far, no explanatory hypotheses have been suggested to account for such observation.

According to the World Health Organization (WHO), a prevalence of nTSH levels ≥ 5 mIU/L below 3% is suggestive of an adequate iodine nutritional status in the population if samples are collected after 72 hours of life.[1] However, as part of screening programs for congenital hypothyroidism, samples are usually collected at 48 hours of life, or even earlier in the case of neonatal discharge, to prevent missed opportunities. This practice is supported by several authors.[11,19] This study did not find significant differences in the percentage of nTSH levels ≥ 5 mIU/L when comparing samples collected before or after 48 hours of life, although other study described such differences.[11]

Although the WHO establishes a cut-off point of nTSH levels at 5 mIU/L to differentiate adequate and deficient iodine levels in a population,[1] a study that assessed pregnant women with adequate iodine levels and TSH levels in their newborn infants reported that the cut-off point for nTSH should be 2.77 mIU/L, lower than what has been proposed by the WHO.[25] Regardless of the cut-off point used, the prevalence of nTSH levels ≥ 5 mIU/L in our study was 9.6%, which suggests the presence of mild ID in the population of La Pampa. Although this study did not cover other indicators of ID, the percentage of nTSH ≥ 5 mIU/L mentioned above emphasizes the need for continuous monitoring of iodine nutritional status in the population, as even the presence of mild ID may result in significant damage to the neurodevelopment and other aspects of child health.[3,7]

The increase in the prevalence of nTSH found in this study (2021–2022) compared to the previous study (2001–2002) is relevant. However, such comparison should be deemed with caution because the first study included only newborn infants from the EALM, while this study included data on TSH levels from newborn infants from the entire province of La Pampa. In spite of the difference in the methodology used, this comparison suggests the possibility of ID re-emergence and increase over time, which has also been reported in other countres.[15–17]

The re-emergence of ID worldwide may be attributed to several causes, including an inadequate iodization of table salt. However, it may also be explained by conflicting public health campaigns. For example, one recommendation is to restrict sodium intake to prevent cardiovascular disease. However, if sodium restriction focuses on suppressing the consumption of table salt, which is the main source of iodine supplementation, it may lead to the failure of the successful public policy of ID prevention. In 2022, the WHO issued a new document with recommendations to avoid this conflict, which is critical in regions with a history of ID and in sensitive stages of life, such as pregnancy and childhood.[18]

The main strength of this study is the high number of nTSH samples analyzed, which were obtained from the public sector throughout the province of La Pampa. The analysis of nTSH databases commonly used to detect congenital hypothyroidism, as used in this study, allowed a rapid and effective monitoring of population iodine nutritional status in several countries.[10–13,26–29] Such methodology may be implemented permanently as a valuable supplement to the PNPN that already exists in our country, with minimum additional costs. To this end, the variables sex and absolute value of nTSH level should be incorporated into the program's database because, until October 2023, sex was not registered and the nTSH level was entered as a category of nTSH (normal, high, or suspicious).

One of the limitations of this study was the use of a single ID indicator, which, for example, hinders the interpretation of a greater prevalence of high nTSH levels in health region 2.

Additional studies underway in La Pampa, including the measurement of other indicators, such as salt iodization, iodine levels in pregnant women, and the incidence of goiter in schoolchildren, together with the use of georeferencing systems and the assessment of endocrine disruptors, may provide greater precision on this aspect in the future, as suggested by other authors.[26,30,31]

CONCLUSIONS

The prevalence of nTSH levels ≥ 5 mIU/L among newborn infants in La Pampa in 2021 and 2022 reached 9.6%, above the 3% threshold established by the WHO and is suggestive of possible mild ID in the population of this province. This prevalence was also higher than that described 20 years ago. No differences were observed in nTSH samples collected before and after the 48 hours of life.

These results underline the need to monitor this condition and highlight the added utility of the PNPN with minimum additional costs. ■

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