



Congenital Hypothyroidism in Preterm Newborns: A Retrospective Study Arising from a Screening Program in Fars Province, Southwestern Iran

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ABSTRACT

Objectives: There is a high interest in the early diagnosis of hypothyroidism in preterm newborns for preventing any intellectual disability. Our study sought to determine the incidence of abnormal thyroid-stimulating hormone (TSH) between three and six days old and in weeks two, six, 10, and 12 after birth to evaluate the validity of repeating the test in premature infants. **Methods:** We conducted a retrospective review of 320 886 live births in Fars province, Southwestern Iran, from March 2014 to October 2017. TSH levels in premature infants were measured by heel prick test, and the data was collected from the central newborn screening center of Fars province. **Results:** The number of premature newborns was 15 381, and the prevalence of hypothyroidism was 2.3%. Among 355 premature newborns with high TSH, 31.3% was detected in three to six days of life, 43.9% in the second week, 14.4% in the sixth week, 9.9% in the tenth week, and 0.6% in the twelfth week as hypothyroidism. **Conclusions:** Our results showed that thyroid screening of preterm infants needs retesting in two, six, and 10 weeks after to detect cases in newborns who would not otherwise be identified.

Congenital hypothyroidism (CHT) results from an absent or under-developed thyroid gland (dysgenesis), or the gland has developed but cannot produce enough thyroid hormone (dysmorphogenesis). Most neonates with CHT have a normal gross appearance on birth; however, a delay in the diagnosis of abnormalities threatens their neurodevelopmental function, especially in preterm and low-birth-weight infants.¹⁻³

Different screening programs were established more than 40 years ago with the purpose of preventing intellectual disability arising from CHT. Screening programs for CHT were first established in North America in 1972, and this program is now performed routinely in most developed countries.^{4,5} Iranian screening programs for CHT were established in 1987⁶ and were included in health care services in 2005. Thyroid-stimulating hormone (TSH) levels determined by filter-paper blood-spot is used preferably for CHT screening in Iran due to its high specificity.^{7,8}

The best time to determine TSH levels is when the neonate is three to six days old, which can minimize the false positive of high TSH due to the

physiological neonatal TSH rise.⁸ Although many centers have recommended repeated screening tests in premature newborns, there is no general agreement on the time of its measurement.

The reported incidence rate of both CHT and preterm infants has increased significantly during the past two decades.⁹ In this study, we evaluated the prevalence of CHT among preterm infants by studying the results of thyroid screening tests in different parts of Fars province, Iran, from 2014 to 2017. Our study sought to determine the incidence of abnormal TSH at three to six days old and in weeks two, six, 10, and 12 to evaluate the validity of repeating the test.

METHODS

This retrospective cross-sectional study recorded all live births in Fars province, Iran, from March 2014 to October 2017. Neonates with a gestational age < 37 weeks were considered premature and included in this study. Any neonates with major congenital anomalies were excluded from the study. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1397.138).

All data, including TSH measurements, were collected from the central newborn screening center of the Shiraz University of Medical Science. TSH was measured from dried blood spots from the newborns' heel on filter paper using commercial enzyme-linked immunosorbent assay (ELISA) kits (NEO-TSH, Pishtaz Teb Zaman Diagnostics) according to the manufacturer's instructions. TSH levels were first measured between three and six days of birth; however, the premature newborns were rescreened in weeks two, six, 10, and 12 after birth. The cut-off for a positive test was ≥ 10.0 mU/L in the first seven days of life and ≥ 5.0 mU/L after seven days in premature infants.¹⁰ We also recorded sex and birth date data. If the results were abnormal, the newborns were referred to an endocrinologist, but we had no information about the follow-up.

The data were analyzed using SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.), and a p -value ≤ 0.050 was considered statistically significant. Chi-square test was used to evaluate the qualitative variables, and McNemar's test was used for comparing the results of different levels of TSH in several times.

RESULTS

From March 2014 to October 2017, 320 886 (48.0% girls and 52.0% boys) live births were screened in Fars province. The number of premature newborns was 15 381 (4.8%); one neonate with Down syndrome was excluded from the study. Three-hundred and fifty-five premature newborns had an abnormal TSH screening test (TSH > 10.0 mU/L in the first week and TSH > 5.0 mU/L after the first week of life) during the 12 weeks follow-up giving a CHT prevalence of 2.3%. There were 195 (54.9%) boys and 160 (45.1%) girls with CHT, and no significant difference was found between boys and girls with prematurity ($p = 0.050$). TSH ranged from 0.1 mU/L to 285.4 mU/L (mean = 6.6 ± 22.4 mU/L) in 355 premature newborns with CHT.

The number of newborns with high TSH levels recorded at three to six days old was 111 giving a 31.3% prevalence of CHT at first screening. Among the remaining 244 premature newborns with CHT; 156 (43.9%) had increased TSH levels in week two, 51 (14.4%) in week six, 35 (9.9%) in week 10, and two (0.6%) newborns in week 12 [Figure 1].

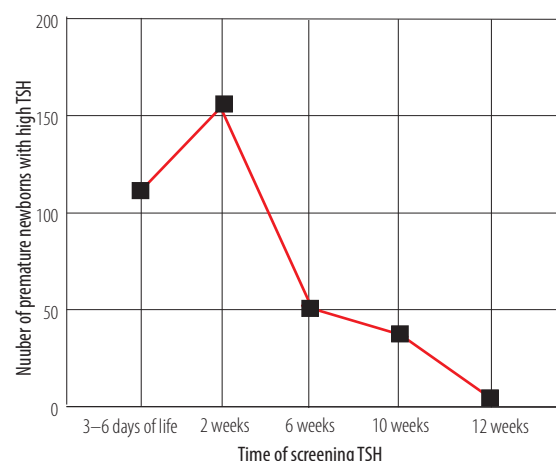


Figure 1: Number of premature newborns with high Thyroid-stimulating hormone (TSH) measure in the first three to six days of life and in weeks two, six, 10, and 12.

McNemar's test showed that the results of the first screening (days three to six) were significantly different with the results of the second test in the second week of life ($p < 0.001$) and with the third test in the sixth week ($p < 0.001$). Current data revealed that 63.9% (156/244) of the premature neonates who had the first negative test had positive second test results.

Among 88 premature newborns with normal TSH at the first screening and in the second week, 51 (58.0%) newborns showed high TSH in the sixth week ($p < 0.001$) post-birth.

DISCUSSION

We found a 2.3% prevalence rate of hypothyroidism in 15 381 premature newborns born in Fars province, Iran, from 2014 to 2017. The rate of CHT was reported as 0.1% in all live births in this area in 2006–2007.¹¹ Many studies found that CHT was more common in premature newborns. This high rate of CHT in premature newborns is explained by immaturity in the hypothalamic-pituitary-thyroid axis, a low thyroidal capacity to synthesize iodine, and immature thyroid hormone metabolism; however, premature newborns also need more thyroid hormone for thermogenesis.¹²

A Korean study found 12.2% (30/246) of very low birth newborns (< 1500 g) exhibited CHT.¹³ Another study from the USA revealed 9.1% of 280 premature infants < 30 weeks gestation had thyroid dysfunction.¹⁴ European studies showed ranges from 5% to 18% of preterm infants with

hypothyroidism.^{15,16} Our study considered only screening data; therefore, we did not have the weight and exact gestational age data for the newborns.

According to our data, the first screening test revealed one-third of premature newborns had CHT. A recent review indicated that many studies emphasized repetition of TSH for proper CHT screening in preterm infants; however, the proper time for retesting is disputed.¹⁷ The number of premature newborns with CHT in our study detected by the second and sixth weeks TSH retesting was 43.9% and 14.4%, respectively, which was significantly increased compared with our first sampling. We recommend repeating TSH testing in the second week of life similar to previous studies^{15,17} and six weeks after birth. Delaying the second and third screening test, and therefore the diagnosis of CHT can threaten the intellectual ability in preterm newborns. Our data found 10.4% of preterm infants (37/355) showed a rise of TSH after the sixth week of life; however, commencing appropriate initial therapy can reduce the pathological consequences of CHT.

Endocrinologists and pediatricians recommended measuring both TSH and free thyroxine for CHT screening in preterm neonates.¹⁸ Therefore, it is advised that primary screening tests and following the tests with both TSH and free thyroxine could diagnose CHT with delayed TSH elevation.

All premature patients were recruited from a screening referral center in Fars province and may not represent premature newborns in other major cities of Iran. Another limitation of our study was a lack of data on the exact gestational age and birth weight of our study cohort.

CONCLUSION

Our report described the prevalence of CHT in premature newborns based on measuring TSH in a large cohort of newborns in Fars province, Iran. The thyroid screening program of preterm infants needs a second (week two), third (week six), and fourth (week 10) screening test for CHT and is essential in detecting newborns who would not otherwise be identified.

Disclosure

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