Arch Iran Med. June 2019;22(6):310-317

http www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

Open Access

Original Article

Audit of the Congenital Hypothyroidism Screening Program in 15 Provinces of Iran

Ladan Mehran, MD[1]; Shahin Yarahmadi, MD[2]; Davood Khalili, MD[3]; Mehdi Hedayati, MD[4]; Atieh Amouzegar, MD[1]; Pouria Mousapour, MD[1]; Nasrin Ajang, MD[2]; Fereidoun Azizi, MD[1*]

[1]Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Endocrinology and Metabolic Office, Center for Disease Control, Ministry of Health and Medical Education, Tehran, Iran
[3]Prevention of Metabolic Disorders Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences & Department of Biostatistics and Epidemiology, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Cellular and Molecular Endocrine Research Center (CMERC), Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: The newborn screening (NBS) program for congenital hypothyroidism (CH) was launched on a national scale in Iran since 2005; we evaluated the program in 15 provinces, from 2011 to 2014.

Methods: Fifteen provinces, including 17 districts, were included in the study. Aggregated data of screening, diagnosis, and management of all neonates born in each district in 2011 were retrospectively gathered and collectively analyzed.

Results: Program coverage ranged from 77 to 100% in different districts. The positive predictive value was low and widely ranged from 1.3 to 15.5. Transient congenital hypothyroidism (TCH) distribution values were over 5 mU/L in more than 3% of the population and were reported in 9 out of 17 districts. Repeated screening test due to inappropriate sampling varied from 0.9% in Lorestan to 36% in Zabol. Recall rate varied from 0.16 in Ardebil to 1.58 in Zanjan. CH incidence was high, with the highest value being observed in Zanjan (1:241 newborns). Screening age at 3–5 days from birth were highly observed in Gonabad (95.2%) and Zanjan (94.5%), with the lowest values observed in Giroft, Zabol, Kerman and Tehran. CH treatment was initiated before 40 days of age in 90.6% of cases. Survival time for TSH normalization event varied among the districts from 25 to 163 days. After withholding treatment at 3 years of age, TCH was identified in 30%–60% of hypothyroid cases.

Conclusion: Main indicators of the screening program have reached the optimal goals defined by the Ministry of Health and Medical Education. However, high false positive rate and non-optimal neonatal TSH distribution values necessitate readdressing these challenging issues.

Keywords: Congenital hypothyroidism, Evaluation, Newborn, Screening

Cite this article as: Mehran L, Yarahmadi S, Davood Khalili D, Hedayati M, Amouzegar A, Mousapour P, Ajang N, et al. Audit of the congenital hypothyroidism screening program in 15 provinces of Iran. Arch Iran Med. 2019;22(6):310–317.

Received: June 28, 2018, Accepted: December 1, 2018, ePublished: June 1, 2019

Introduction

Congenital hypothyroidism (CH), as the most common congenital endocrine disorder, is an avoidable cause of growing neurological disabilities and mental retardation, which has an increased global prevalence.[1,2] CH has been found to be considerably prevalent in Iran; that is, many times higher than its worldwide statistics.[3,4] Screening newborns for CH has made it possible to detect and treat the affected neonates, prevent irreversible neurologic outcomes and promote intelligence quotient of the patients; thereby minimizing the burden of the disease and its related costs.

The newborn screening (NBS) program has been instituted since 2005 in all provinces of Iran. This program comprises measurement of thyroid stimulating hormone (TSH) during 3 to 5 days from birth, implementing strategies in the diagnosis, management and follow-up of affected neonates up to 3 years, while educating their parents.[5,6]

Ultimate goals of any screening program in coverage, screening age, recall rate, compliance to follow-up and treatment of affected newborns, may virtually depend on both the screening system and the characteristics of the population under screening. These features may vary in each region, influence the effectiveness of the program, and consequently the overall screening results. Hence, it is essential to evaluate the program individually in each region in order to achieve national optimal goals. Herein, by conducting a 3-year retrospective cohort study on children born in 2011, we aimed to evaluate the effectiveness of the NBS program and assess the final results of the program in each of the seventeen university districts of Iran, separately.

***Corresponding Author:** Fereidoun Azizi, MD; Professor of Internal Medicine and Endocrinology, Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, I.R.Iran. P.O. Box: 19395-4763, Tehran, I.R. Iran. Phone: + 98 21 22432503; Fax: + 98 21 22402463; Email: azizi@endocrine.ac.ir

Materials and Methods

In Iran, the Ministry of Health and Medical Education (MOH) is responsible for nationwide health service and research; and health care is under coverage of universities of medical sciences in each region. Data of the NBS program are routinely recorded in relevant forms by technical experts in charge of screening centers and collected in databases of universities. These forms, provided by MOH, include birth date, sex, consanguinity, type of delivery, sampling date, results of neonatal screening and diagnostic tests, time of treatment initiation and follow-up data. All neonates born in 2011, from 17 districts in 15 provinces including: Zanjan, Semnan, Tehran, Lorestan, Hormozgan, Markazi, Alborz, Birjand, Kordestan, Golestan, Ardebil, North Khorasan (Bojnoord), Sistan and Baloochestan(Zabol), Razavi Khorasan (Sabzevar, Gonabad) and Kerman (Kerman, Giroft) were included in this 3 year retrospective cohort study. The sampling at each district was based on census and all live births entered the study. The aggregated data were extracted from the pooled database which were routinely recoded in the forms provided by MOH for the NBS program. From 51 university districts in 2011, we evaluated 17 districts (one-third of sample size) from 15 provinces (out of 31 provinces at that time) which approximates to one third of live births (501 726 live births out of 1 382 229 live births reported by national registry in Iran in 2011). Sampling unit in this study is university district and not individual neonates. We did not analyze raw data from neonates, but gathered aggregated data stored in health deputies in each university district. Based on the main program objectives of screening coverage which is ideal if over 90% of live birth are screened in each region and the following formula considering Z = 1.64, d = 10%, P = 90% and N = 51 (total number of university district), the sufficient sample size is 18 district and we evaluated 17 districts.

$$n = \frac{Z^2 P(1-P)}{d^2(1+\frac{n}{N})}$$

National CH screening initiates with a TSH measurement from the heel prick blood spot in neonates. The protocol is completely described in the national guideline.[7]

According to the screening protocol , neonates with a Guthrie TSH test ≥5 mU/L on the first TSH screening test, are recalled for complementary tests; of whom, those with TSH 5–9.9 mU/L are recalled to repeat the screening test, and those with TSH ≥ 10 mU/L are recalled for confirmatory venous sampling. TSH screening is measured by Eliza, and serum levels of TSH and T4 are respectively measured by IRMA and RIA methods, with Kavoshiar diagnostic kits (Tehran, Iran). The neonates detected to have hypothyroidism were referred to an endocrinologist for treatment, with the goal of normalizing serum T4 during the first 2 weeks, and serum TSH within the first month after treatment.

Definitions

The recall rate is defined as the percentage of neonates who are recalled for confirmatory venous tests, regardless of the screening steps, including those with first TSH screening ≥10 mU/L and second TSH screening ≥5 mU/L.

The project coverage percentage is defined as the proportion of total live births who underwent screening; it is ideal if over 90% of live births are screened in each region. Birth before 37 weeks of pregnancy is considered as prematurity. Low birth weight is defined as birth weight under 2500 grams. Consanguinity is defined as the neonate's parents being siblings. Ideal objectives of all indicators have been described in the national guideline.[7] Hypothyroidism is defined as having TSH > 10 mU/L and T4 <6.5 µg/dL.

Transient congenital hypothyroidism (TCH) refers to a temporary deficiency of thyroid hormone which recovers later in infancy, and is mostly identified after treatment withdrawal at 3 years of age. Permanent CH is defined as the persistence of thyroid hormone deficiency even after withdrawal therapy.

Statistical Analysis

Continuous variables have been presented as means (SD) for normal, and median (IQR) for skewed variables; and variables with categorical distribution as numbers and percentages. CH incidence rates were calculated as number of confirmed CH among all live births during one year as well as numbers of CH per 1000 live births (95% CI). Survival analysis was performed by Kaplan-Meier to find the time period for TSH normalization event or censoring of individuals, which was defined as the time between the initiation of treatment and TSH normalization event or the censoring of individuals due to loss to follow-up, death or ending of study without TSH normalization, whichever happened first. Event time was measured based on the time of the scheduled visits. SPSS version 16 was used for data analysis, and P values ≤ 0.05 were considered as statistically significant.

Results

In total, 501 726 live births were reported in the selected regions in 2011; of whom 90.3% were screened for CH, and 0.23% of the screened (1073) were confirmed as having CH. CH subjects were followed up for 3 years. Table 1 shows the baseline characteristics of the CH patients in each region.

Table 2 shows the outline of the screening procedure, including number of live births, program coverage, recall rates, false positive, positive predictive value of the screening test and CH incidence, in 17 districts separately. CH incidence varied from highest in Zanjan (1:241) to lowest in Bojnoord (1:1666).

Program coverage was 100% in Zanjan, Sabzevar, Semnan, Gonabad, Markazi, Golestan and Ardebil and

Table 1. Baseline Characteristics of Patients With Congenital Hypothyroidism

Region*	CH Patients (n)	Boys (%)	Girls (%)	Birth Weight (g)	Birth Height (cm)	Normal Delivery (%)	Consanguinity (%)	Family History of Thyroid Disorders (%)	Congenital Anomaly (%)
Giroft	20	55	45	3061 ± 576	48.4 ± 2	70	60	16.7	11.1
Zabol	16	68	32	2865 ± 668	48.9 ± 3	87	87	6.3	18.8
Zanjan	77	48	52	3117 ± 465	49.5 ± 3	70	19	6.5	6.5
Sabzevar	24	54	46	3170 ± 536	50.0 ± 2	70	33	8.4	12.5
Semnan	17	24	76	2879 ± 635	47.7 ± 5	41	23	5.9	5.9
Kerman	82	57	43	2902 ± 708	48.8 ± 3	50	41	9.1	2.7
Tehran	316	51	49	3131 ± 539	49.2 ± 3	55	35	8.3	2.2
Gonabad	6	50	50	2800 ± 700	46.7 ± 3	80	40	1.0	0
Lorestan	105	49	51	3043 ± 616	48.8 ± 4	52	43	6.7	1.9
Hormozgan	50	66	34	2911 ± 559	48.3 ± 3	69	42	8.0	6.0
Markazi	72	47	53	2922 ± 663	49.3 ± 2	53	28	7.0	4.2
Alborz	74	54	46	3145 ± 536	50.1 ± 3	39	33	18.9	1.4
Birjand	45	56	44	3086 ± 596	42.3 ± 2	54	62	9.8	4.5
Kordestan	80	62	38	3181 ± 553	48.9 ± 2	70	20	6.8	4.2
Golestan	56	57	43	3363 ± 589	49.1 ± 3	59	23	5.1	0
Ardebil	33	61	39	3171 ± 594	48.9 ± 2	36	44	6.6	3.1
Total	1073	53	47	3086 ± 586	49 ± 3	43	35	18.6	5.6

*Regions mean the areas under coverage of a medical university, data were not available for Bojnoord.

was the lowest (77%) in Zabol, totally accounts for 90.3% (95% CI: 90.2–90.4). 3.5 %(95% CI: 3.41–3.52) with TSH values over 5 mU/L were recalled for more evaluation. The overall recall rate for confirmatory venous sampling was 0.69% (95% CI: 0.64–0.70); the range varied from lowest in Ardebil (0.16%) to highest in Zanjan (1.58%). CH incidence was estimated to be 1:462 live births (95% CI; 1:460:1; 463) or 2.2 per 1000 live births (95% CI: 2.0–2.3).

In total population positive predictive value (PPV) was 6.9 (95% CI: 6.5–7.3) with the highest and lowest values in Gonabad (15.5) and Bojnoord (1.3), respectively.

Table 3 shows the screening age (data for Sabzevar, Hormozgan and Kordestan were not available); the most appropriate statistics for screening at 3–5 days from birth, were observed in Gonabad (95.2%) and Zanjan (94.5%); while Giroft, Zabol, Kerman and Tehran had the worst statistics, with the lowest belonging to Giroft (58.7%).

According to Table 4, TSH distribution value ≥ 5 mU/L in more than 3% of neonates, was observed in Sabzevar, Kerman, Tehran, Lorestan, Markazi, Birjand, Kordestan and Bojnoord. Birjand had the highest rate of abnormal TSH results.

The main objective of the CH screening program is the time of treatment initiation (Table 5; data for Bojnoord was not available). The most favorable results were observed in Kordestan, in which treatment for 91.3% of the affected neonates had initiated within 28 days; while in Giroft and Kerman only 40% of the affected neonates had been treated before the 28th day of life. On the other hand, there were no CH subjects treated after 41 days from birth, in Sabzevar and Ardebil, while 35.7% of the affected neonates in Semnan started treatment after 41 days from birth.

The screening test was repeated in 11.2% of neonates, due to inappropriate sampling, hospital admission, blood exchange, special drug consumption, prematurity, low birth weight or birth weight ≥4000, multiple pregnancy, special hospital admission, blood exchange, or drug consumption. Gonabad had the highest rate (20.5 %), mostly due to TSH values of 5–9.9 mU/L as well as hospital admission. Repeated screening due to inappropriate sampling was mostly observed in Zabol, Tehran, Bojnoord, Alborz and Giroft, respectively (Table 6; data for Sabzevar, Hormozgan and Kordestan were not available).

Follow-up data in Bojnoord, Zabol and Kordestan were not available, so 977 out of 1073 CH neonates were followed. Of 977 patients, 742 had first event of TSH normalization, 227 were lost to follow-up (184 after starting treatment and 43 neonates in following visits), one neonate was censored due to death before TSH normalization event and 7 neonates were censored due to no event of TSH normalization till the end of study. After initiating treatment, the shortest mean period of time for TSH to decrease to its normal range, was detected in Lorestan (32 days); whereas the longest period was in Alborz (163 days) (Table 2). After three years of follow-up, 449 (9.42%) and 598 (1.57%) of neonates were diagnosed with transient and persistent CH, respectively (Table 2). Information on the final outcomes was missing in 38 neonates.

Discussion

The current retrospective cohort study provides comprehensive evaluation of the congenital screening

Table 2. Program Coverage, Recall Rate, Positive Predictive Value (PPV) and Incidence in 17 Regions of Iran in 2011

Region[a]	Live Birth (*n*)	Screening (*n*)	Program Coverage (%)	TSH Screening ≥ 5 mU/L (%)	Recall Rate (%)	PPV[b]	CH (*n*)	False Positive (*n*)	CH Incidence[c]		Type of CH		Time to TSH Normalization
									1:Live birth	/1000	Transient *n*(%)	Permanent *n*(%)	Day
Giroft	13397	12509	93	1.7	0.32	9.4	20	193	1:670	1.5	9(45)	11(55)	73(33-133)
Zabol	12900	9895	77	1.2	0.26	13.5	16	103	1:806	1.2	8(53.3)	7(46.7)	—
Zanjan	18525	20422	100	4.1	1.58	9.2	77	760	1:241	4.2	31(40.3)	46(59.7)	42(34-49)
Sabzvar	9425	9425	100	3.5	0.67	7.2	24	306	1:393	2.5	12(50)	12(50)	34(26-41)
Semnan	6398	7694	100	1.6	0.45	13.8	17	106	1:376	2.7	8(47.1)	9(52.9)	50(32-67
Kerman	34050	27445	81	3.0	0.78	9.9	82	741	1:415	2.4	42(53.2)	37(46.8)	40(26-53)
Tehran	153176	123329	80	4.5	1.05	5.7	316	5234	1:485	2.1	103(33.2)	207(66.8)	45(40-49)
Gonabad	2098	2156	100	1.8	0.19	15.5	6	33	1:350	2.9	3(50)	3(50)	25(18-31)
Lorestan	35799	33506	93.5	5.1	0.82	6.2	106	1603	1:338	3.0	48(49.5)	49(50.5)	32(25-38)
Hormozgan	34712	30209	87	2.8	0.55	5.9	50	796	1:694	1.4	23(47.9)	25(52.1)	45(32-57)
Markazi	22596	22603	100	3.2	0.96	9.9	72	651	1:314	3.2	46(64.8)	25(35.2)	36(32-39)
Alborz	38391	34191	89	2.2	0.63	9.8	74	678	1:519	1.9	29(39.7)	44(60.3)	163(108-217)
Birjand	14561	14479	99.4	5.2	0.97	5.9	45	708	1:324	3.1	20(45.5)	24(54.5)	36(24-47)
Kordestan	25584	24560	95.9	4.5	0.88	7.2	80	1025	1:320	3.1	37(47.4)	41(52.6)	—
Golestan	39154	40268	100	1.8	0.35	7.7	56	669	1:699	1.4	17(30.4)	39(69.6)	48(29-66)
Ardebil	22631	23934	100	1.0	0.16	13.9	33	206	1:686	1.5	13(40.6)	19(59.4)	77(24-129)
Bojnoord	18329	16293	88.9	5.0	0.58	1.3	11	804	1:1666	0.6	—	—	—
Total[d]	**501726**	**452918**	**90.3 95% CI: 90.2–90.4**	**3.5 95% CI: 3.41–3.52**	**0.69 95%CI: 0.64–0.70**	**6.9 95% CI: 6.5–7.3**	**1085**	**14616**	**I:462 95% CI: 1:460:1;463**	**2.2 95%CI: 2.0–2.3**	**449(42.9)**	**598(57.1)**	**45 95% CI: 41–48**

[a] Regions mean the areas under coverage of a medical university; [b] positive predictive value: PPV, [c] CH Incidence expressed by the number of confirmed CH newborns among all live births during 1 year and number of confirmed CH newborns per 1000 live births; [d] Total refers to total number or average value based on data in each column.

Table 3. Neonatal Age at Screening, in 14 Regions of Iran in 2011

Region*	Neonatal Age at Screening (Days After Birth)		
	3–5 (%)	6–21 (%)	22 (%)≥
Giroft	58.7	40.4	0.8
Zabol	71.9	26.9	1.2
Zanjan	94.5	5.2	0.3
Semnan	79.4	19.0	1.6
Kerman	73.8	24.5	1.7
Tehran	75.2	22.1	2.7
Gonabad	95.2	4.2	0.6
Lorestan	77.1	21.5	1.4
Markazi	77.2	21.9	0.8
Alborz	72.8	24.7	3.5
Birjand	81.2	17.9	0.9
Golestan	81.9	16.8	1.3
Ardebil	76.5	22.6	0.8
Bojnoord	79.3	18.7	2.0
Total	**78.1**	**20.5**	**1.4**

*Regions mean the areas under coverage of a medical university; data for Sabzevar, Hormozgan and Kordestan were not available; The ideal objective of this indicator is that at least 65% of the neonates be screened at 3–5, 25% between 6–21 days and 10% ≥22 days after birth.

Table 4. TSH Distribution Values at Screening, in 17 Regions of Iran in 2011

Region*	TSH Distribution Values (mU/L)			
	Under 5 (%)	5–9.9 (%)	10–19.9 (%)	≥20 (%)
Giroft	98.23	1.59	0.08	0.09
Zabol	98.58	1.27	0.10	0.03
Zanjan	95.80	3.90	0.20	0.10
Sabzevar	96.50	3.10	0.23	0.10
Semnan	98.29	1.49	0.15	0.05
Kerman	96.82	3.06	0.06	0.04
Tehran	95.46	3.96	0.46	0.09
Gonabad	98.19	1.76	0.00	0.04
Lorestan	94.87	4.61	0.39	0.11
Hormozgan	97.20	2.70	0.08	0.02
Markazi	96.60	3.40	0.20	0.10
Alborz	97.62	1.93	0.33	0.10
Birjand	94.71	4.94	0.24	0.09
Kordestan	95.50	4.20	0.27	0.01
Golestan	98.23	1.59	0.11	0.07
Ardebil	98.90	0.95	0.02	0.06
Bojnoord	95.04	4.54	0.36	0.04
Total	96.77	2.88	0.26	0.09

*Regions mean the areas under coverage of a medical university; TSH ≥ 5 mU/L in more than 3% of screened neonates indicates iodine deficiency in the region, as this indicator has been known as one of the evaluation indicators of national salt iodization program by WHO.

program in 17 university districts of Iran. Mean values of the most important indicators were acceptable within the ideal objectives determined by the Ministry of Health and Medical Education. Distribution of the TSH levels was out of the acceptable range and implied iodine deficiency in a few regions.

Although the mean program coverage was superior to 90%, this rate varied from 77 to 100% in different regions;

Table 5. Time of treatment initiation in 16 regions of Iran in 2011

Region*	Time of Treatment Initiation (Days After Birth)		
	Under 28 (%)	28–40 (%)	≥ 41(%)
Giroft	40.0	40.0	20.0
Zabol	75.0	12.5	12.5
Zanjan	87.0	11.7	1.3
Sabzevar	45.8	54.2	0
Semnan	50.0	14.3	35.7
Kerman	40.3	37.7	22.1
Tehran	72.3	20.1	7.6
Gonabad	50.0	16.7	33.3
Lorestan	61.2	27.2	11.7
Hormozgan	54.0	28.0	18.0
Markazi	73.6	19.4	6.9
Alborz	80.8	12.3	6.8
Birjand	58.1	32.6	9.3
Kordestan	91.3	3.80	5.0
Golestan	78.2	12.7	9.1
Ardebil	81.8	18.2	0
Total	**69.6**	**21.0**	**9.4**

*Regions mean the areas under coverage of a medical university; data for Bojnoord were not available; Treatment initiation before 40 days following birth in 90% of affected neonates is the ideal goal of this indicator.

Gonabad had a coverage rate of 100% and Zabol had the lowest coverage amongst all districts (77%). Therefore, wise approaches must be considered to find a solution to promote the program coverage in districts which coverage was lower. Most developed countries have reported coverage rates up to 99%.[8,9] In other developing countries, lower rates than Iranian rates have been reported[10]; these differences may be due to lack of a registration system in developing countries; however, in Iran, this barrier has been resolved due to comprehensive education of mothers during pregnancy.

Rate of repeated screening due to inappropriate sampling varied from 2.2% in Gonabad to 36% in Zabol; in this regard, educating and updating the technicians and providing well equipped screening settings require more attention.

The screening age varied widely in different districts; in Gonabad 95.2% of the neonates were screened during the 3rd to 5th day from birth; where Giroft and Zabol had the worst statistics. Screening before 48 hours from birth may lead to false positive results. The American academy of Pediatrics recommends screening between 48 hours to 4 days from birth and before nursery discharge.[11] In Iran, despite early discharge of mothers, sufficient maternal awareness of screening importance results in screening at the appropriate neonatal age.

Early detection and treatment is a fundamental factor when dealing with CH. Former studies have reported the importance of early scheduled treatment initiation in order to prevent mental and developmental defects.[12,13] The neonatal age for treatment initiation was not acceptable in Giroft, Semnan, Gonabad and Kerman. According to prior studies, detection and initiation of treatment for neonates

Table 6. The Frequency of Causes of Repeated Screening Test, in 14 Regions of Iran in 2011

Region*	Inappropriate Sampling, No. (%)	TSH 5–9.9, No. (%)	Prematurity, No. (%)	Birth Weight ≤2500 g, No. (%)	Multiple Pregnancy, No. (%)	Birth Weight ≥4000 g, No. (%)	Hospital Admission, No. (%)	Blood Exchange, No. (%)	Special Drug Consumption, No. (%)	Total, No. (%)
Giroft	95 (12.7)	216 (28.8)	30 (4)	148 (19.7)	80 (10.6)	7 (0.9)	172 (22.9)	0	0	748 (5.6)
Zabol	179 (36)	100 (20)	9 (1.8)	110 (22.1)	58 (11.6)	16 (3.2)	25 (5)	(0)	(0)	497 (5)
Zanjan	211 (6.3)	820 (24.5)	150 (4.5)	329 (9.8)	215 (6.4)	113 (3.3)	1511 (45)	1 (0.02)	0	3350 (16.1)
Semnan	19 (2.2)	79 (9.5)	51 (6.1)	110 (13.2)	106 (12.7)	60 (7.2)	397 (47.7)	3 (0.3)	6 (0.7)	831 (10.8)
Kerman	119 (4.9)	946 (39.1)	174 (7.1)	892 (36.8)	17 (0.7)	190 (7.8)	81 (3.3)	0	0	2419 (8.8)
Tehran	4511 (26.1)	4411 (28.3)	74 (4.3)	1466 (8.2)	1669 (9.6)	987 (5.9)	2999 (16.9)	17 (0.08)	6 (0.05)	16813 (13.7)
Gonabad	0	38 (8.6)	78 (17.6)	67 (15.1)	50 (11.3)	76 (17.1)	134 (30.2)	0	0	443 (20.5)
Lorestan	28 (0.9)	822 (26.8)	220 (7.2)	328 (10.6)	626 (20.3)	217 (7)	820 (26.7)	5 (0.1)	3 (0.09)	3069 (9.1)
Markazi	78 (2.1)	701 (19.2)	327 (8.9)	425 (11.6)	484 (13.3)	363 (9.9)	1257 (34.5)	1 (0.02)	0	3636 (16)
Alborz	362 (14.5)	542 (21.8)	141 (5.6)	318 (12.8)	436 (17.5)	206 (8.3)	474 (19.1)	1 (0.04)	0	2480 (7.1)
Birjand	94 (3.6)	685 (26.9)	156 (6.1)	673 (26.4)	194 (7.6)	161 (6.3)	699 (27.5)	13 (0.5)	2 (0.07)	2677 (18.4)
Golestan	332 (10)	630 (19.1)	126 (3.8)	427 (12.9)	360 (10.9)	378 (11.4)	1039 (37.5)	1 (0.03)	0	3293 (8.1)
Ardebil	160 (7.2)	226 (10.2)	163 (7.3)	149 (6.7)	361 (16.3)	126 (5.7)	1015 (45.9)	8 (0.3)	0	2208 (9.2)
Bojnoord	198 (19.5)	504 (49.7)	55 (5.4)	78 (7.6)	37 (3.6)	54 (5.3)	53 (5.2)	30 (2.9)	5 (0.4)	1014 (6.2)
Total	**6386 (14.6)**	**10720 (24.6)**	**2427 (5.5)**	**5520 (12.6)**	**4693 (10.7)**	**2954 (6.7)**	**10676 (24.5)**	**80 (0.2)**	**22 (0.05)**	**43478 (11.2)**

*Regions mean the areas under coverage of a medical university; data for Sabzevar, Hormozgan and Kordestan were not available.

before 10 to 13 days, and normalization of TSH levels before 3 weeks of age, have been effectively beneficial.[14,15] Hashemipour et al have assessed the congenital screening program in Isfahan, during 2002–2009; in which the program coverage was 96.6% and the prevalence of hypothyroidism was estimated to be 1:420. Treatment was initiated at 22.9 ± 13.2 days from birth, and in 93.7% of the population, before 45 days.[16] Other studies have demonstrated the mean age of treatment initiation in different countries began, within 11 ± 5 days in Wales,[17] 17 days in England,[18] 10.3 days in Saudi Arabia[19] and 22.8 ± 6.8 in France.[20]

The goal of therapy is to normalize T4 within 2 weeks and TSH within one month. Studies show that optimal therapy normalizes serum T4 within 3 days and TSH within 2–4 weeks. In the current study, time for TSH normalization was too high in a few regions, which may be due to inappropriate drug dosage or non–compliance to treatment. In one study, infants with thyroid function normalization after 2 weeks had significantly lower cognitive attention and mental abilities, compared to those who achieved normal thyroid function before 2 weeks of treatment [21]. Rapid normalization of serum T4 is critical for optimal neurodevelopmental outcome; however, we could not calculate the time for T4 normalization in this study.

Despite global achievements in screening of CH, recall rate and high PPV still remain an issue. According to past reports, recall rates have been widely different from 0.01% to 13.3%. The wide range could be due to different screening strategies (using TSH, T4 or both), laboratory techniques, sampling site (umbilical cord, heel or veins), recall indicators, human errors, and regional or cultural factors.[22-25]

Mean TSH over 5 mU/L in more than 3% of neonates was observed in 9 out of 17 districts, which may indicate iodine deficiency (IDD), based on the WHO suggestion.[26] Iran was announced to be IDD free since 2000, and monitoring surveys performed every five years indicated iodine sufficiency[27]; however, the trend of population median urinary iodine (MUI) was decreasing over time and a national survey reported iodine deficiency in pregnant women.[28] Also, a few studies showed iodine deficiency in some parts of Iran. These evidence could justify the higher neonatal TSH values in a few districts of Iran, despite population iodine sufficiency e.g. in Sabezvar, Zanjan, Kerman, Tehran and Markazi; with population MUI ≥ 100μg/L, while having TSH values over 5 mU/L in more than 3% of population (Table 2). Iodine supplementation for pregnant women could improve neonatal TSH and reduce recall rate. The presence of iodine deficiency in pregnant women, despite population iodine sufficiency, has also been reported in other developed countries.[29,30]

Applying of optimal recall criteria would reduce recall rate and false positive results, while provides good coverage of neonatal screening programs; this is of great importance, as response to recall may be poor, especially in Asian populations; and higher numbers of false-positive results impose a great challenge in the risky communication with parents, an aspect of NBS which has been highly ignored. Lower false positive results improve the cooperation of parents with physicians and their assurance, while minimizing stress in families; also, managing the costs of the project by reducing unnecessary repeated laboratory

tests and excess workload for staff.

The strategy of adopting a second screening test in neonates with TSH of 5–9.9 leads to eliminate unnecessary venous sampling and saves costs. A study by Yarahmadi et al has also confirmed the cost-effectiveness of the current cut-off point for the screening test.[31] Although considering higher TSH cut-off points lowers the costs, the rate of missing affected newborns may increase in this case.

High prevalence of CH in Iran was mainly due to the transient form of the disease.[32,33] Usually, transient hypothyroidism includes 10%–15% of all hypothyroidism cases.[34] Higher rates of transient hypothyroidism may be as a result of the following factors: iodine insufficiency or toxicity, passing of thyroid-blocking antibodies from maternal circulation, usage of anti-thyroid or goitrogen drugs or topical antiseptic agents rich in iodine, very low birth weight or immature births, gene mutations, incomplete iodine organization, or increase of anti-thyroid auto-antibodies production. In Lebanon, high prevalence of hypothyroidism may be due to both iodine insufficiency and consanguinity.[35] Without doubt, more investigations are needed to unfold the exact reasons of transient hypothyroidism, especially regarding higher concentrations of autoantibodies in iodine-sufficient regions.[36] Moreover, iodine toxicity must be considered as an important cause of transient hypothyroidism.[5] A study by Ordookhani et al, has revealed that most of the transient cases were associated with elevated urine iodine levels.[37] We also found higher rates of persistent hypothyroidism in Iran compared to other countries; this rate was reported as 1:1800 in Greece, 1:1400 in Saudi Arabia, and 1:2384 in Turkey.[38-40]

In a 3-year retrospective cohort, we investigated a large population from different regions and assessed many aspects of the screening program. The narrow CIs for the main objectives found for the main objectives in this study is indicative of high precision and sufficient sample size (more than one third of live births in 2011). The limitation was high loss in follow-up at the screening centers, which could be justified by the participants quitting the health system and referring to private sectors, particularly in big cities, and thus their follow-up data were missed. Furthermore, we did not evaluate the final outcome (final IQ and developmental status) in neonates who were screened, diagnosed and treated.

In conclusion, main indicators of the screening program have reached the optimal goals defined by the Ministry of Health and Medical Education although it needs promotion to higher standards. High false positive rates and non-optimal neonatal TSH distribution values necessitate addressing these challenging issues by conducting studies on the effect of iodine status and specificity and sensitivity of the current screening cut-off point. TSH values over 5 mU/L in more than 3% of neonates, despite sufficient iodine status of the population in some areas, may be due to iodine deficiency in pregnant women. Recommendation of iodine supplementation in pregnant women could help to reduce neonatal TSH and false positive results in the screening test.

Authors' Contribution

LM: Designing and writing the manuscript; SY: Program manager, national data gathering for congenital hypothyroidism screening program; DK: Data analysis and writing the manuscript; MH: writing the manuscript; AA: Writing the manuscript; PM: writing the manuscript; NA: Program coordinator, National data gathering; FA: Designing and writing the manuscript.

Conflict of Interest Disclosures

None.

Ethical Statement

Written consent was obtained from all participants, and the study was approved by the institutional ethics committee of Research Institute for Endocrine Sciences (RIES) of Shahid Beheshti University of Medical Sciences.

References

1. Deladoëy J, Van Vliet G. The changing epidemiology of congenital hypothyroidism: fact or artifact? Expert Rev Endocrinol Metab. 2014;9(4):387-395. doi: 10.1586/17446651.2014.911083.
2. Deladoey J, Ruel J, Giguere Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Quebec. J Clin Endocrinol Metab. 2011;96(8):2422-9. doi: 10.1210/jc.2011-1073.
3. Ordookhani A, Mirmiran P, Hajipour R, Hedayati M, Azizi F. Screening for congenital hypothyroidism in the Islamic Republic of Iran: strategies, obstacles and future perspectives. East Mediterr Health J. 2002;8(4-5):480-9.
4. Mehrnejat N, Yazdanpanah H, Fadaei Nobari R, Hashemipour M, Maracy M, Moafi M, et al. Spatial Analysis of Neonatal Congenital Hypothyroidism and Nitrate as an Environmental Pollutant in Isfahan Province During 2010-2013. Int J Prev Med. 2015; 6:76. doi: 10.4103/2008-7802.162952.
5. Shamshiri AR, Yarahmadi S, Forouzanfar MH, Haghdoost AA, Hamzehloo G, Holakouie Naieni K. Evaluation of current guthrie TSH cut-off point in Iran congenital hypothyroidism screening program: a cost-effectiveness analysis. Arch Iran Med. 2012;15(3):136-41.
6. Karamizadeh Z, Dalili S, Sanei-Far H, Karamifard H, Mohammadi H, Amirhakimi G. Does congenital hypothyroidism have different etiologies in Iran? Iran J Pediatr. 2011;21(2):188-92.
7. Yarahmadi S. National screeining program for congenital hypothyroidism, physician guideline. Tehran: Javan, 2012.
8. Ades AE, Walker J, Jones R, Smith I. Coverage of neonatal screening: failure of coverage or failure of information system. Arch Dis Child. 2001;84(6):476-9. doi: 10.1136/adc.84.6.476.
9. Verkerk PH, Derksen-Lubsen G, Vulsma T, Loeber JG, de Vijlder JJ, Verbrugge HP. Evaluation of a decade of neonatal screening for congenital hypothyroidism in The Netherlands [in Dutch]. Ned Tijdschr Geneeskd. 1993;137(43):2199-205.
10. Dabbous NI, Abd El-Aziz HM, Abou El-Enein NY, Kandil HH, El-Kafoury AA. Indicators of the screening program for congenital hypothyroidism in Alexandria. J Egypt Public Health Assoc. 2008;83(3-4):307-27.
11. American Academy of Pediatrics AAP Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health: Newborn screening for congenital hypothyroidism: recommended guidelines. Pediatrics. 1993;91(6):1203-9.
12. Kempers MJ, van der Sluijs Veer L, Nijhuis-van der Sanden MW,

Kooistra L, Wiedijk BM, Faber I, et al. Intellectual and motor development of young adults with congenital hypothyroidism diagnosed by neonatal screening. J Clin Endocrinol Metab. 2006;91(2):418-24. doi: 10.1210/jc.2005-1209.
13. Bain P, Toublanc JE. Adult height in congenital hypothyroidism: prognostic factors and the importance of compliance with treatment. Horm Res. 2002;58(3):136-42. doi: 10.1159/000064489.
14. Bongers-Schokking JJ, de Muinck Keizer-Schrama SM. Influence of timing and dose of thyroid hormone replacement on mental, psychomotor, and behavioral development in children with congenital hypothyroidism. J Pediatr. 2005;147(6):768-74. doi: 10.1016/j.jpeds.2005.09.031.
15. Donaldson M, Jones J. Optimising outcome in congenital hypothyroidism; current opinions on best practice in initial assessment and subsequent management. J Clin Res Pediatr Endocrinol. 2013;5(Suppl 1):13-22. doi: 10.4274/jcrpe.849.
16. Hashemipour M, Dehkordi EH, Hovsepian S, Amini M, Hosseiny L. Outcome of congenitally hypothyroid screening program in isfahan: iran from prevention to treatment. Int J Prev Med. 2010;1(2):92-7.
17. Law WY, Bradley DM, Lazarus JH, John R, Gregory JW. Congenital hypothyroidism in Wales (1982-1993): demographic features, clinical presentation and effects on early neurodevelopment. Clin Endocrinol (Oxf). 1998;48(2):201-7. doi: 10.1046/j.1365-2265.1998.00379.x.
18. Tillotson SL, Fuggle PW, Smith I, Ades AE, Grant DB. Relation between biochemical severity and intelligence in early treated congenital hypothyroidism: a threshold effect. BMJ. 1994;309(6952):440-5. doi: 10.1136/bmj.309.6952.440.
19. Henry G, Sobki SH, Othman JM. Screening for congenital hypothyroidism. Saudi Med J. 2002;23(5):529-35.
20. Léger J, Larroque B, Norton J; Association Française pour le Dépistage et la Prévetion des Handicaps de l'Enfant. Influence of severity of congenital hypothyroidism and adequacy of treatment on school achievement in young adolescents: a population-based cohort study. Acta Paediatr. 2001;90(11):1249-56. doi: 10.1111/j.1651-2227.2001.tb01570.x.
21. Selva KA, Harper A, Downs A, Blasco PA, Lafranchi SH. Neurodevelopmental outcomes in congenital hypothyroidism: comparison of initial T4 dose and time to reach target T4 and TSH. J Pediatr. 2005;147(6):775-80. doi: 10.1016/j.jpeds.2005.07.024.
22. Chanoine JP, Boulvain M, Bourdoux P, Pardou A, Van Thi HV, Ermans AM, et al. Increased recall rate at screening for congenital hypothyroidism in breast fed infants born to iodine overloaded mothers. Arch Dis Child. 1988;63(10):1207-10. doi: 10.1136/adc.63.10.1207.
23. Harris P, Dreyfus NG. Newborn thyroid screening in a municipal hospital. Am J Dis Child. 1982;136(3):248-50.
24. Walfish PG. Evaluation of three thyroid-function screening tests for detecting neonatal hypothyroidism. Lancet. 1976;1(7971):1208-10. doi: 10.1016/S0140-6736(76)91732-3.
25. Wu LL, Sazali BS, Adeeb N, Khalid BA. Congenital hypothyroid screening using cord blood TSH. Singapore Med J. 1999;40(1):23-6.
26. World Health Organization. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers; 2007. Available from: https://apps.who.int/iris/handle/10665/43781
27. Azizi F, Mehran L, Sheikholeslam R, Ordookhani A, Naghavi M, Hedayati M, et al. Sustainability of a well-monitored salt iodization program in Iran: marked reduction in goiter prevalence and eventual normalization of urinary iodine concentrations without alteration in iodine content of salt. J Endocrinol Invest. 2008;31(5):422-31. doi: 10.1007/BF03346386.
28. Delshad H, Touhidi M, Abdollahi Z, Hedayati M, Salehi F, Azizi F. Inadequate iodine nutrition of pregnant women in an area of iodine sufficiency. J Endocrinol Invest. 2016;39(7):755-62. doi: 10.1007/s40618-016-0438-4.
29. Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merrill L, Moye J. Iodine status in pregnant women in the National Children's Study and in U.S. women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. Thyroid. 2013;23(8):927-37. doi: 10.1089/thy.2013.0012.
30. Fuse Y, Shishiba Y, Irie M. Gestational changes of thyroid function and urinary iodine in thyroid antibody-negative Japanese women. Endocr J. 2013;60(9):1095-106.
31. Yarahmadi S, Tabibi S, Alimohammadzadeh K, Ainy E, Gooya M, Mojarrad M, et al. Cost–Benefit and Effectiveness of Newborn Screening of Congenital Hypothyroidism: Findings from a National Program in Iran. International Journal of Endocrinology and Metabolism. 2010;8(1):1-6.
32. Hashemipour M, Amini M, Talaie M, Kelishadi R, Hovespian S, Iranpour R, et al. Parental consanguinity among parents of neonates with congenital hypothyroidism in Isfahan. East Mediterr Health J. 2007;13(3):567-74.
33. Rosenthal M, Addison GM, Price DA. Congenital hypothyroidism: increased incidence in Asian families. Arch Dis Child. 1988;63(7):790-3. doi: 10.1136/adc.63.7.790.
34. Connelly JF, Coakley JC, Gold H, Francis I, Mathur KS, Rickards AL, et al. Newborn screening for congenital hypothyroidism, Victoria, Australia, 1977-1997. Part 1: The screening programme, demography, baseline perinatal data and diagnostic classification. J Pediatr Endocrinol Metab. 2001;14(9):1597-610. doi: 10.1515/JPEM.2001.14.9.1597.
35. Kulaylat NA, Najjar SS. Transient primary hypothyroidism in prematures. Clin Pediatr (Phila). 1987;26(7):339-42. doi: 10.1177/000922888702600703.
36. Kahaly GJ, Dienes HP, Beyer J, Hommel G. Iodide induces thyroid autoimmunity in patients with endemic goitre: a randomised, double-blind, placebo-controlled trial. Eur J Endocrinol. 1998;139(3):290-7.
37. Ordookhani A, Pearce EN, Mirmiran P, Azizi F, Braverman LE. Transient congenital hypothyroidism in an iodine-replete area is not related to parental consanguinity, mode of delivery, goitrogens, iodine exposure, or thyrotropin receptor autoantibodies. J Endocrinol Invest. 2008;31(1):29-34. doi: 10.1007/BF03345563.
38. Skordis N, Toumba M, Savva SC, Erakleous E, Topouzi M, Vogazianos M, et al. High prevalence of congenital hypothyroidism in the Greek Cypriot population: results of the neonatal screening program 1990-2000. J Pediatr Endocrinol Metab. 2005;18(5):453-61. doi: 10.1515/JPEM.2005.18.5.453.
39. al-Jurayyan NA, Shaheen FI, al-Nuaim AA, el-Desouki MI, Faiz A, al Herbish AS, et al. Congenital hypothyroidism: increased incidence in Najran province, Saudi Arabia. J Trop Pediatr. 1996;42(6):348-51. doi: 10.1093/tropej/42.6.348.
40. Kempers MJ, Lanting CI, van Heijst AF, van Trotsenburg AS, Wiedijk BM, de Vijlder JJ, et al. Neonatal screening for congenital hypothyroidism based on thyroxine, thyrotropin, and thyroxine-binding globulin measurement: potentials and pitfalls. J Clin Endocrinol Metab. 2006;91(9):3370-6. doi: 10.1210/jc.2006-0058.