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A 7-year study on the prevalence of congenital hypothyroidism in northern Iran

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Abstract

Background: Congenital hypothyroidism (CH) is one of the most common congenital endocrine disorders. The present study determined the prevalence and demographic characteristics of congenital hypothyroidism in the north of Iran.

Objective: To determine the prevalence of congenital hypothyroidism based on transient and permanent types with demographic characteristics in Mazandaran province in northern Iran.

Methods: This retrospective descriptive survey analyzed the medical records of children with primary diagnosis of CH in health centers in all cities of Mazandaran Province between June 2009 and March 2016. To compare the study groups (CH type) in terms of quantitative and qualitative variables, the t-test and Chi-square test were used, respectively using the SPSS22. P-value <0.05 was considered as significant.

Results: Of 269,088 infants screened during the study period, 548 infants with primary congenital hypothyroidism were identified (a prevalence of 1 per 491 births) and congenital hypothyroidism was definitively diagnosed in 389 children (a prevalence of 1 per 453 births); of them, 169 had permanent CH (a prevalence of 1 per 1043 births) and 220 had transient CH (a prevalence of 1 per 801 births). The female to male ratio in the permanent congenital hypothyroidism group was higher than that in the transient congenital hypothyroidism group (p=0.08). The family relationship between mother and father was stronger in the permanent congenital hypothyroidism group than in the transient congenital hypothyroidism group (p=0.03).

Conclusion: These findings show that congenital hypothyroidism is more prevalent in the north of Iran than in other areas of Iran; the prevalence of transient CH is particularly higher than permanent CH.

Keywords: Neonate screening, Congenital hypothyroidism, Permanent, Transient

1. Introduction

Congenital hypothyroidism (CH), with a prevalence of 1 per 3,000 to 4,000 births (1), is one of the most common congenital endocrine disorders (2). It is a major cause of preventable mental retardation and is divided into transient and permanent types (3). In transient hypothyroidism, infants have normal or low serum thyroxine (T4) (4) and increased serum thyroid-stimulating hormone (TSH) concentrations that may be restored with or without treatment (5), while patients with the permanent type require lifetime hormone therapy (6). Since early diagnosis and treatment of CH results in normal childhood in many cases of hypothyroidism (7), screening of infants is important (8). The screening for CH is considered a remarkable medical achievement and must be performed in every region of the world due to different prevalence rates and the impact of varying environmental factors (7). CH screening was first performed in Quebec, Canada in 1974 (9) and was recommended by the American Academy of Pediatrics in 1993 when it was found that the prevalence varies in different geographical areas (10). For example, a 20-year study reported prevalence rates of 1 per 10,000 births in France (11) and 1 per 4,094 births in the USA in 1987, which increased to 1 per 2,372 births in 2002 (6). Screening was implemented as a pilot study in Iran in 1987 but was discontinued due to iodine deficiency in the country. After the elimination of the iodine deficiency, screening began

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again in Tehran and Damavand in 1997 (12). Screening continued in other regions of Iran, and the reported prevalence rates of CH in 2008 were 1 per 914 live births in Tehran (13), 1 per 357 live births in Isfahan (14), and 1 per 625 live births in Mazandaran; these rates are much higher than those reported worldwide (15). However, some questions about the epidemiology of CH remain unanswered, including the distribution of permanent and transient cases (16). Since most recent studies have shown high prevalence rates in some areas of Iran (15, 17), this retrospective study aimed to examine the prevalence and demographic characteristics of CH in the north of Iran.

2. Material and Methods

2. 1. Study design

This descriptive retrospective study determined the prevalence of congenital hypothyroidism based on transient and permanent types with demographic characteristics in Mazandaran Province in northern Iran from June 2009 to March 2016.

2. 2. Procedure

After receiving project approval from the Vice Chancellor for Research at our institution and receiving permission from the Ethics Committee of the university, the researcher was introduced by the Vice Chancellor for Health to the health centers of all cities in north of Iran (Mazandaran Province) in order to obtain access to the medical records of all children diagnosed with CH. In case of missing information, the researcher called the infants' families or invited them to visit health centers in order to complete the medical records. In some cases, the patients had been referred to the private clinics of physicians in other cities or provinces after diagnosis or for continuing treatment, so their medical records were incomplete because the families did not have access to the information. Other information obtained from the patients' files included child's sex, gestational age at birth, delivery type, number of twins, family relationship between mother and father, existence of similar diseases in the family, weight, height, and head circumference of the child from birth to 5 years of age, child's abnormalities, values of the first and second heel prick tests, the values of venous tests, age at onset of treatment, the initial dose of hormone used in infancy, the time after which the tests became normal after hormone therapy, hypothyroidism type.

Most of the medical records had been filed based on the Protocol of the Iranian Ministry of Health (18). The first heel prick test was performed in all infants born alive on their 3rd-5th days after birth. TSH levels were measured from samples collected on filter papers from the heel pricks. Infants with TSH levels ≥5-9.9 mill units per liter (mU/L) were recalled for a second heel prick test on the 8th-14th days after birth. If the TSH levels were ≥5-19.9 mU/L, they were referred for venous blood sampling to measure the levels of TSH, Triiodothyronine resin uptake (T3RU), and T4/Free T4. Infants with TSH levels ≥20 mU/L, in addition to venous blood sampling, were immediately started on treatment with levothyroxine without waiting for the test results. The TSH cut-off concentration is 5 mU/L in Iran. Therefore, according to the Ministry of Health's guideline on screening in Iran, all infants with venous TSH values above this cutoff were diagnosed with primary hypothyroidism and treated with levothyroxine (10-15 µg/kg/day) by the focal point physician. The aim was to provide a treatment based on the Iranian neonatal screening program and to normalize T4 and TSH levels within 2 weeks and one month, respectively (18). Accordingly, the infants were first followed-up two weeks after starting treatment, then every month during the first six months of life, then every two months during the second six months, and finally every three months from one to three years of age. After three years, the drug dosage was reduced by half or discontinued; TSH and T4 tests were performed after 4 weeks in order to differentiate transient and permanent hypothyroidism cases. According to the national protocol, subsequent hormone tests were repeated 2-3 months later and then annually. If the clinical examinations and the serum TSH and T4 levels of these children were normal after discontinuation of the drug, they were diagnosed with transient hypothyroidism and asked to visit the focal point physician at certain intervals for testing and examination of the thyroid status. Otherwise, they were diagnosed with permanent hypothyroidism and were required to undergo lifetime thyroid scanning hormone therapy. According to the protocol, the definitive diagnosis of CH is determined at the end of three years of age. Since the definitive diagnosis of hypothyroidism for children had been confirmed until March 2014, the actual prevalence of CH among children born in the north of Iran was determined until that time.

The mean and standard deviation were used to describe the quantitative data, and the frequency (percentage) was used to describe the qualitative variables. To compare the study groups (CH type) in terms of quantitative and qualitative variables, the t-test and chi-square test were used, respectively. Binary logistic regression was applied to examine the simultaneous correlation between the CH type and the variables studied. All variables that were correlated with CH type at a significance level of below 0.2 in the univariate analysis were entered into the model.

Statistical analyses were performed using SPSS-22 and the P value less than 0.05 was considered statistically significant and the P value less than 0.1 was considered marginally significant.

3. Results

Screening was performed in northern Iran from June 2009 to March 2016; a total of 269,088 live newborns underwent CH screening, and 548 infants were diagnosed with primary hypothyroidism (1 per 491 births). Eight infants (1.5%) died before the diagnosis of CH type. Diagnosis of CH type was impossible for seven infants (1.3%) due to migration, and for other two infants because their parents did not cooperate with the health centers. Eighty infants (14.8%) were born before 37 weeks of gestation. Six infants were born with Down syndrome, five with cardiac anomalies, one with skeletal abnormality, and two with hearing impairment. Five infants had dysfunctions in more than two organ systems. There were 37 sets of twins, of whom 16 had hypothyroidism (both twins), and 3 sets of triplets, of whom two infants in one set of triplets were diagnosed with hypothyroidism. The growth status of children with CH showed that 65.7% were in good condition in terms of physical growth, 13.1% had slow growth, and 6.6% were overweight. About 176,250 infants were screened through March 2014, and the CH type was definitively diagnosed in 389 children (a prevalence of 1 per 453 births), 169 of whom had permanent CH (a prevalence of 1 per 1043 births), and 220 had transient CH (a prevalence of 1 per 801 births). The comparison of basic clinical and demographic characteristics of infants with CH in terms of CH type is presented in Table 1. The mean birth weight of the group with permanent CH was higher than that in the group with transient CH (p=0.09), while the normal weight gain in the group with permanent CH was less than that in the group with transient CH (p=0.04). The female to male ratio in the permanent group was higher than that in the transient group (p=0.08). The results showed that the rate of Cesarean section in the group with permanent CH was higher than that in the group with transient CH (p=0.03). In addition, the family relationship between mother and father in the group with permanent CH was stronger than that in the transient group (p=0.03). The results showed that TSH levels in the first heel prick test and first venous draw and the initial dosage of medicine prescribed in infants with permanent CH were significantly higher than those in the transient group (p<0.05). In the next stage and after controlling for the effect of the variables entered into the multivariate analysis model, a significant correlation was observed between CH type and primary venous TSH values and Cesarean delivery (Table 2).

Table 1. Demographic and clinical characteristics of permanent and transient congenital hypothyroidism

Variables		Type of CH			p-value
		Permanent CH	Transient CH	Pending	
Gender (F/M)		82/87 (0.9)	90/130 (0.7)	72/69 (1.04)	0.08
Weight (gr)		3202±629.14	3085.7±711.2	3093.9±692.5	0.09
Height (cm)		49.1±3.53	49±3.8	49.4±5.3	0.72
Head Circumference (cm)		34.5±1.8	34.1±2.37	34.2±2.1	0.15
Normal growth		111 (31)	140 (39.1)	107 (29.9)	0.043
Maturity, n (%)		120 (72.3)	148 (74)	98 (72.1)	0.4
Singleton, n (%)		160 (95.2)	191 (91.4)	127 (91.4)	0.29
Type of Delivery, n (%)	C/S	114 (68.3)	119 (58.3)	94 (67.6)	0.03
	Vaginal	53 (31.7)	85 (41.7)	45 (32.4)	
Parental Consanguinity, n (%)	Near relative	11 (6.6)	23 (11.1)	11 (7.9)	0.03
	Distant relative	45 (26.9)	35 (16.8)	15 (10.7)	
	Not relative	113 (66.86)	162 (73.63)	133 (83.65)	
History of Thyroid Disorder	Mother	0	4	1	NA
	Father	8	11	9	
	Siblings	4	1	2	
Mean TSH level (mIU/L)	1st sample TSH	41.1±48.3	18.8±30.5	34.3±50.1	<0.001
	2nd sample TSH	10.4±5.3	9.7±4.1	14.7±31.7	0.73
	1st venous sample TSH	55±51.4	22.7±27.8	47.7±51.6	<0.001
Mean venous total T4 level (µg/dl)		7.5±15.6	7.8±6.9	8.8±12.9	0.8
Mean Age when treatment started (day)		28.3±61.4	28±29.4	24±25.8	0.95
First L-thyroxin dosage (µg/kg/day)		12±3.7	11.1±3.5	11.8±3.5	0.01

Table 2. Association between kind of CH and independent variables in Multiple Logistic Regression Model.

Variables	OR (%95: CI)	SE	p-value
Venous TSH	0.976 (0.969-0.984)	0.004	<0.0001
Type of Delivery(C/S)	0.608 (0.375-0.986)	0.247	0.044

OR: Odds ration; SE: Standard error

4. Discussion

In this study, the prevalence rate of CH in the north of Iran was estimated as 1 per 491 live births, which is very high compared to those reported for other countries in Asia (19), Europe (20), and America (21). High prevalence rates have been reported for certain neighboring countries of Iran; however, these rates are lower than those in this study. For example, the CH prevalence rates are 1 per 650 births in Turkey (22), 1 per 1,600 births in Pakistan (23), and 1 per 3,692 births in Saudi Arabia (24). In recent decades, an increase in the prevalence of CH has been observed in some countries (25, 26); however, the prevalence of CH in Iran is higher than in other countries (17, 27, 28). It should be noted that the TSH cut-off point at the beginning of screening was >15-25 mU/L in some countries, but has decreased in recent years. This change may contribute to the increased prevalence in recent years (27). However, the cut-off point is ≥5 mU/L in Iran, even in the first heel prick test on the 3rd and 5th days after birth (29). The prevalence rates of CH differ in various regions of Iran. For example, the reported rates were 1 per 307 in Markazi Province (28), 1 per 666 live births in East Azerbaijan (17), 1 per 1,465 live births in Shiraz from southern cities (30), and 1 per 1,608 live births in Yazd from the central cities of the country (31). These differences cannot be attributed to the differences in screening practices because screening is performed according to a mandatory protocol organized by the Ministry of Health in Iran; TSH concentration is evaluated using an enzyme-linked immunosorbent assay (ELISA)-based method, since distributing and accessing laboratory ELISA test kits is easier and cheaper compared to radioimmunoassay kits. The TSH screening cut-off value is ≥5 mU/L in all areas of Iran to prevent the occurrence of false negatives (32). It appears that the southern provinces of the country with warmer climate have fewer cases of CH.

The results of this study and other studies which have been conducted in Iran in recent years clearly show that the increased prevalence of CH is associated with the increased prevalence of transient CH (2). This study reported a 56.6% prevalence of transient CH, a rate which is markedly different to that for Fars (46.4%) (30) and Isfahan (79.4%) provinces (2, 3). However, the prevalence is similar to that reported in the neighboring province of Gilan (56.8%) (33). Reports suggest that the prevalence of transient CH in most cases is 10-15% higher than that of permanent CH (16). The reported prevalence rates are much lower in some countries, such as the USA (28%) (21), Egypt (17.7%) (16), and France (38%) (11), compared to the rate observed in the present study. The causes of permanent CH are mostly related to inappropriate growth or ectopic thyroid gland (16), while there are different causes for transient CH. In addition to genetic and environmental factors (34), the other main causes include maternal TSH receptor-blocking antibodies, exposure to local iodine, maternal use of anti-thyroid medications (35), iodine deficiency, increased iodine, consumption of goitrogens, infants with very low weight (<1500 g), premature infants (less than 37 weeks); in some cases the causes are unknown (13, 14, 36). Iodine deficiency has not been detected in Iran since 1977 (2). In a study of three provinces of Iran, Azizi et al. reported that the use of iodized salt by Iranian households and the elimination of iodine deficiency may not be enough for pregnant women and may cause specific problems associated with iodine deficiency (37). Some countries still attribute CH to iodine deficiency (16). Ordookhani et al. attributed transient CH to iodine contamination and increased urinary iodine. However, they found no statistically significant correlation between the transient CH and normal groups, as well as between gender, family relationship of parents, delivery type, and consumption of goitrogens and drugs. Therefore, they attributed transient CH mostly to environmental and genetic factors (36). Hashemipour conducted a study of 69 children with CH and a control group in Isfahan in 2010 and identified increased iodine as a reason for the increased prevalence of CH (38), but this finding has not been confirmed by other studies in Iran (39). Hashemipour conducted a study on a small sample size years after iodized salt consumption in the country; however, it is the most recent study on this subject. Therefore, there is a need for studies on larger groups in different regions of Iran, particularly in terms of iodine consumption, urinary iodine level, and other environmental and immunological factors in order to identify the causes of increased CH in Iran, particularly in northern Iran.

In this study, 43.4% of cases diagnosed with CH in northern Iran were of permanent type (1 in every 1,043 births), a prevalence rate higher than that of other regions of the world. The reported prevalence of permanent CH is 1 per 2,320 births in Italy (40) and 1 per 2,367 births in Argentina (8). This difference may be due to environmental, genetic, and immunological differences (16). Other studies from different parts of Iran have reported prevalence

rates of permanent CH of 1 per 581 births in Markazi Province (28), 1 per 1,133 births in Isfahan (3) and 1 per 3,537 births in Yazd (31). According to these studies, the prevalence of CH varies among different races and ethnicities (27) and is higher in Asian infants than in others. One of the main reasons for the high CH prevalence in Iran is the high rate of consanguineous marriages (41). However, the results of this study showed that 70.7% of the parents of the infants with CH had no family relationship with each other in the north of Iran but the distant family relationship in the permanent group was significantly higher than that in the transient group.

In this study, the female/male ratio was 0.8 to 1. Generally, in Iranian studies, the female/male ratio is lower in the transient CH group (2). Several studies conducted in European countries, Australia, and Canada have reported female/male ratios as high as 2 to 1 (26). However, recent studies have reported ratios of 1.56 to 1 in the USA (26), and 2.5 to 1 in Australia (42) which are not consistent with our study. The reason why women rather than men are more prone to CH is unknown (43). However, according to Hinton, the prevalence of CH in male infants is higher than female infants in some races and ethnicities (25). The female/male ratio for CH varies in different regions of Iran. For example, the reported ratios are 0.7 in Isfahan (14), 1.19 in Shiraz (30), and most of the male patients belonged to the transient group. In this study, the female/male ratios in the transient and permanent groups were 0.7 (90:130) and 0.9 (82:87), respectively. The difference between the two groups was not statistically significant. The number of male infants born with CH in Iran in recent years is higher than that of female infants, a difference more prevalent in the transient group. This difference can be clearly seen in studies in some areas of Iran, particularly in a study by Ghasemi that reported female/male ratios of 0.7 and 1.01 in the transient and permanent groups, respectively (2), as well as Hashemipour's study, which reported an estimated female/male ratio of 0.7 in both transient and permanent groups (14). Therefore, due to the increased number of male infants with CH in recent years, further research on the genetic and environmental factors is necessary.

In this study, two-thirds of infants diagnosed with CH were born by Cesarean section (59% of permanent cases and 41% of transient cases). However, the Cesarean rate in Iran is much higher than that worldwide (44). A study reported a rate in Tehran hospitals over 50%, which is very different from the World Health Organization (WHO) estimate of 15% (45). The study by McElduff et al. suggested that Cesarean delivery increases TSH levels in newborns compared with those of vaginal delivery (46), but Ordookhani and Ghasemi observed no correlation between delivery type and CH (2, 36). Since the use of iodized topical antiseptics is inevitable in surgeries, it is expected that the number of infants with transient CH will increase in Iran. In this study, infants with permanent CH were mostly born by Cesarean section compared to the transient type, a statistically significant difference. Given that this research was based on medical records, further studies are necessary.

The mean TSH levels obtained from the first heel prick and venous sampling in patients with permanent CH were significantly higher than those of patients with transient CH. The same result was also observed in studies conducted by Bekhit in Egypt (16) and Hashemipour in Isfahan (3). In this study, although the mean birth weight of the permanent group was more than that of the transient group, weight gain in the permanent group was less than that in the transient group. This finding is consistent with that reported by Feizi in 2013. This study compared the growth of children with CH to that of normal children, observing that while patient growth improved with age, it was still lower than that of unaffected children (47). However, comparisons were not made between the permanent and transient groups. Dalili (2014) also found no difference between the control and experimental groups in terms of growth status (33). Thus, it seems that the growth of children with CH depends on factors such as the dose of levothyroxine and the age at onset of treatment (48). In the present study, the mean drug dose administered and the age at onset of treatment were similar in both groups and no significant difference was observed. Among all patients diagnosed with CH in this area, 44 received treatments later than others due to false negative results; because they were older at the time of diagnosis, they received lower initial doses of medication. The physical and mental status of these 44 children is being followed up.

5. Study strengths and limitations

The strengths of our study were as follows: the results obtained are related to a long period of 7 years, i.e. from the beginning of CH screening to 2012 in Mazandaran Province and to determine the exact prevalence of CH, all cases born in the province, even those who migrated from the province, or were referred to private sector for treatment, or did not cooperate with the researcher, as well, those who died were also taken into consideration. Since it was based on medical records and the secondary data and accessing to all samples was not possible, the researcher could not have access to these children to investigate the causes of the disease in the incomplete record files in the health

centers for various reasons, such as patients' migration to other cities, families' non-cooperation with the health care system, and patients' referral to the private sector for treatment or diagnosis of hypothyroidism type.

6. Conclusions

Results of this study, similar to other studies conducted in other areas of Iran, showed that the prevalence of transient and permanent hypothyroidism is very high in northern Iran particularly the prevalence of transient CH which is more prevalent than permanent CH. Therefore, there are factors affecting the development of transient CH and its higher incidence. Regarding the high prevalence of types of hypothyroidism in Mazandaran Province, and considering that early detection and timely treatment will prevent mental retardation, it is therefore necessary to continue to strengthen the screening program.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

References:

1) Kliegman RM, Stanton BF, Geme JW, Schor NF, Behrman RE. Nelson Textbook of Pediatrics. 19 ed: Philadelphia: Sunders Elsevier; 2011.
2) Ghasemi M, Hashemipour M, Hovsepian S, Heiydari K, Sajadi A, Hadian R, et al. Prevalence of transient congenital hypothyroidism in central part of Iran. J Res Med Sci. 2013; 18(8): 699-703. PMID: 24379847, PMCID: PMC3872610.
3) Hashemipour M, Ghasemi M, Hovsepian S, Heiydari K, Sajadi A, Hadian R, et al. Prevalence of Permanent Congenital Hypothyroidism in Isfahan-Iran. Int J Prev Med. 2013; 4(12): 1365-70. PMID: 24498491, PMCID: PMC3898441.
4) Fisher DA, Grueters A. Sperling: Pediatric Endocrinology. 3 ed. Philadelphia: Sunders-Elsevier; 2008.
5) Bhavani N. Transient congenital hypothyroidism. Indian J Endocrinol Metab. 2011; 15(Suppl 2): S117-20. PMID: 21966647, PMCID: PMC3169860.
6) Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis. 2010; 5: 17. doi: 10.1186/1750-1172-5-17. PMID: 20537182, PMCID: PMC2903524.
7) Gruters A, Jenner A, Krude H. Long-term consequences of congenital hypothyroidism in the era of screening programmes. Best Pract Res Clin Endocrinol Metab. 2002; 16(2): 369-82. doi: 10.1053/beem.2002.0202. PMID: 12064898.
8) Chiesa A, Prieto L, Mendez V, Papendieck P, Calcagno Mde L, Gruneiro-Papendieck L. Prevalence and etiology of congenital hypothyroidism detected through an argentine neonatal screening program (1997-2010). Horm Res Paediatr. 2013; 80(3): 185-92. doi: 10.1159/000354409. PMID: 24008435.
9) Ordookhani A, Mirmiran P, Najafi R, Hedayati M, Azizi F. Congenital hypothyroidism in Iran. Indian journal of pediatrics. 2003; 70(8): 625-8. PMID: 14510082.
10) 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. PMID: 8502532.
11) Gaudino R, Garel C, Czernichow P, Leger J. Proportion of various types of thyroid disorders among newborns with congenital hypothyroidism and normally located gland: a regional cohort study. Clinical endocrinology. 2005; 62(4): 444-8. doi: 10.1111/j.1365-2265.2005.02239.x. PMID: 15807875.
12) Azizi F. Screening for congenital hypothyroidism: Late start but promising. Iranian Journal of Endocrinology and Metabolism. 2004; 6(1): 1-3.
13) Ordookhani A, Mirmiran P, Walfish PG, Azizi F. Transient neonatal hypothyroidism is associated with elevated serum anti-thyroglobulin antibody levels in newborns and their mothers. J Pediatr. 2007; 150(3): 315-7. doi: 10.1016/j.jpeds.2006.11.034. PMID: 17307555.

14) Hashemipour M, Hovsepian S, Kelishadi R, Iranpour R, Hadian R, Haghighi S, et al. Permanent and transient congenital hypothyroidism in Isfahan-Iran. J Med Screen. 2009; 16(1): 11-6. doi: 10.1258/jms.2009.008090. PMID: 19349525.
15) Akha O, Shabani M, Kowsarian M, Ghafari V, Sajadi Saravi S. Prevalence of congenital hypothyroidism in Mazandaran Province, Iran, 2008. Journal of Mazandaran University of Medical Sciences. 2011; 21(84): 63-70.
16) Bekhit OE, Yousef RM. Permanent and transient congenital hypothyroidism in Fayoum, Egypt: a descriptive retrospective study. PloS one. 2013; 8(6): e68048. doi: 10.1371/journal.pone.0068048. PMID: 23840807, PMCID: PMC3695950.
17) Zeinalzadeh AH, Talebi M. Neonatal screening for congenital hypothyroidism in East Azerbaijan, Iran: the first report. Journal of medical screening. 2012; 19(3): 123-6. doi: 10.1258/jms.2012.012024. PMID: 23060475.
18) Yarahmadi SH. program of screening for congenital hypothyroidism (CH) in Iran. In: center cd, editor: Ministry of Health, Treatment and Medical Education of Iran; 2012.
19) Gu X, Wang Z, Ye J, Han L, Qiu W. Newborn screening in China: phenylketonuria, congenital hypothyroidism and expanded screening. Ann Acad Med Singapore. 2008; 37(12 Suppl): 107-4. PMID: 19904469.
20) Kumorowicz-Czoch M, Tylek-Lemanska D, Starzyk J. Thyroid dysfunctions in children detected in mass screening for congenital hypothyroidism. J Pediatr Endocrinol Metab. 2011; 24(3-4): 141-5. doi: 10.1515/jpem.2011.080. PMID: 21648281.
21) Mitchell ML, Hsu HW, Sahai I. The increased incidence of congenital hypothyroidism: fact or fancy? Clinical endocrinology. 2011; 75(6): 806-10. doi: 10.1111/j.1365-2265.2011.04128.x. PMID: 21623857.
22) Dilli D, Czbas S, Acican D, Yamak N, Ertek M, Dilmen U. Establishment and development of a national newborn screening programme for congenital hypothyroidism in Turkey. J Clin Res Pediatr Endocrinol. 2013; 5(2): 73-9. doi: 10.4274/Jcrpe.929. PMID: 23748057. PMCID: PMC3701925.
23) Afroze B, Humayun KN, Qadir M. Newborn screening in Pakistan - lessons from a hospital-based congenital hypothyroidism screening programme. Ann Acad Med Singapore. 2008; 37(12 Suppl): 114-3. PMID: 19904471.
24) Abduljabbar M, Al Shahri A, Afifi A. Is umbilical cord blood total thyroxin measurement effective in newborn screening for hypothyroidism? Journal of medical screening. 2009; 16(3): 119-23. doi: 10.1258/jms.2009.009035. PMID: 19805752.
25) Hinton CF, Harris KB, Borgfeld L, Drummond-Borg M, Eaton R, Lorey F, et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. Pediatrics. 2010; 125 Suppl 2: S37-47. doi: 10.1542/peds.2009-1975D. PMID: 20435716.
26) Parks JS, Lin M, Grosse SD, Hinton CF, Drummond-Borg M, Borgfeld L, et al. The impact of transient hypothyroidism on the increasing rate of congenital hypothyroidism in the United States. Pediatrics. 2010; 125(Suppl 2): S54-63. PMID: 20435718.
27) Ford G, LaFranchi SH. Screening for congenital hypothyroidism: a worldwide view of strategies. Best Pract Res Clin Endocrinol Metab. 2014; 28(2): 175-87. doi: 10.1016/j.beem.2013.05.008. PMID: 24629860.
28) Dorreh F, Chaijan PY, Javaheri J, Zeinalzadeh AH. Epidemiology of congenital hypothyroidism in Markazi Province, Iran. J Clin Res Pediatr Endocrinol. 2014; 6(2): 105-10. PMID: 24932604, PMCID: PMC4141571.
29) 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. doi: 012153/AIM.006. PMID: 22369300.
30) Karamizadeh Z, Dalili S, Sanei-Far H, Karamifard H, Mohammadi H, Amirhakimi G. Does congenital hypothyroidism have different etiologies in iran? Iranian journal of pediatrics. 2011; 21(2): 188-92. PMID: 23056786, PMCID: PMC3446167.
31) Ordooei M, Rabiei A, Soleimanizad R, Mirjalili F. Prevalence of Permanent Congenital Hypothyroidism in Children in Yazd, Central Iran. Iranian journal of public health. 2013; 42(9): 1016-20. PMID: 26060662. PMCID: PMC4453880.
32) Osooli M, Haghdoost A, Yarahmadi S, Foruzanfar M, Dini M, Holakouie Naieni K. Spatial Distribution of Congenital Hypothyroidism in Iran using Geographic Information System. IRJE. 2009; 5(1): 1-8.

33) Dalili S, Rezvani SM, Dalili H, Mohtasham Amiri Z, Mohammadi H, Abrisham Kesh S, et al. Congenital hypothyroidism: etiology and growth-development outcome. Acta medica Iranica. 2014; 52(10): 752-6. PMID: 25369009.
34) Monroy-Santoyo S, Ibarra-Gonzalez I, Fernandez-Lainez C, Greenawalt-Rodriguez S, Chacon-Rey J, Calzada-Leon R, et al. Higher incidence of thyroid agenesis in Mexican newborns with congenital hypothyroidism associated with birth defects. Early human development. 2012; 88(1): 61-4. doi: 10.1016/j.earlhumdev.2011.07.009. PMID: 21816548.
35) Eugster EA, LeMay D, Zerin JM, Pescovitz OH. Definitive diagnosis in children with congenital hypothyroidism. J Pediatr. 2004; 144(5): 643-7. doi: 10.1016/j.jpeds.2004.02.020. PMID: 15127002.
36) 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. Journal of endocrinological investigation. 2008; 31(1): 29-34. PMID: 18296902.
37) Azizi F, Aminorroya A, Hedayati M, Rezvanian H, Amini M, Mirmiran P. Urinary iodine excretion in pregnant women residing in areas with adequate iodine intake. Public health nutrition. 2003; 6(1): 95-8. PMID: 12581471.
38) Hashemipour M, Nasri P, Hovsepian S, Hadian R, Heidari K, Attar HM, et al. Urine and milk iodine concentrations in healthy and congenitally hypothyroid neonates and their mothers. Endokrynologia Polska. 2010; 61(4): 371-6. PMID: 20806181.
39) Ordookhani A, Pearce EN, Hedayati M, Mirmiran P, Salimi S, Azizi F, et al. Assessment of thyroid function and urinary and breast milk iodine concentrations in healthy newborns and their mothers in Tehran. Clinical endocrinology. 2007; 67(2): 175-9. doi: 10.1111/j.1365-2265.2007.02857.x. PMID: 17465994.
40) Olivieri A, Fazzini C, Medda E. Multiple Factors Influencing the Incidence of Congenital Hypothyroidism Detected by Neonatal Screening. Horm Res Paediatr. 2015; 83(2): 86-93. doi: 10.1159/000369394. PMID: 25572470.
41) 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. PMID: 17687829.
42) Kurinczuk JJ, Bower C, Lewis B, Byrne G. Congenital hypothyroidism in Western Australia 1981-1998. J Paediatr Child Health. 2002; 38(2): 187-91. doi: 10.1046/j.1440-1754.2002.00812.x. PMID: 12031004.
43) Medda E, Olivieri A, Stazi MA, Grandolfo ME, Fazzini C, Baserga M, et al. Risk factors for congenital hypothyroidism: results of a population case-control study (1997-2003). Eur J Endocrinol. 2005; 153(6): 765-73. PMID: 16322381.
44) Ahmad-Nia S, Delavar B, Eini-Zinab H, Kazemipour S, Mehryar AH, Naghavi M. Caesarean section in the Islamic Republic of Iran: prevalence and some sociodemographic correlates. East Mediterr Health J. 2009; 15(6): 1389-98. PMID: 20218129.
45) Laluei A, Kashanizadeh N, Teymouri M. The Influence of Academic Educations on Choosing Preferable Delivery Method in Obstetrics Medical Team: Investigating their Viewpoints. Iranian Journal of Medical Education. 2009; 9(1): 69-78.
46) McElduff A, McElduff P, Wiley V, Wilcken B. Neonatal thyrotropin as measured in a congenital hypothyroidism screening program: influence of the mode of delivery. J Clin Endocrinol Metab. 2005; 90(12): 6361-3. PMID: 16144951.
47) Feizi A, Hashemipour M, Hovsepian S, Amirkhani Z, Kelishadi R, Yazdi M, et al. Growth and specialized growth charts of children with congenital hypothyroidism detected by neonatal screening in isfahan, iran. ISRN endocrinology. 2013.
48) Aronson R, Ehrlich RM, Bailey JD, Rovet JF. Growth in children with congenital hypothyroidism detected by neonatal screening. J Pediatr. 1990; 116(1): 33-7. PMID: 2295962.