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# Congenital hypothyroidism in different cities of the Isfahan province: A descriptive retrospective study

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## Abstract:

**BACKGROUND:** Considering the high prevalence rate of congenital hypothyroidism CH in Iran, an epidemiological study in each region would be helpful in understanding the etiology of the disorder and providing preventative strategies in this field. This study aims to determine the prevalence of CH in different cities of the Isfahan province.

**MATERIALS AND METHODS:** This descriptive and retrospective study was conducted among 918 primarily diagnosed CH neonates, who have been identified through the neonatal screening program from 2009 to 2015. At the age of  $\geq 3$  years, treatment was discontinued for 4 weeks, and T4 and thyroid-stimulating hormone were measured. Permanent (PCH) or transient (TCH) was determined from the results of the thyroid function tests.

**RESULTS:** From 389,101 screened neonates, 918 were diagnosed with primary CH. The overall prevalence rate of CH was 2.36 in 1000 live birth (ranged 1.58–7.22 in 1000 live birth in different cities). The highest prevalence rate of CH was reported in Ardestan, Khansar, Golpaygan, and Nain cities with prevalence rate of 4.86–7.22 in 1000 live birth and lowest prevalence occurring in Fereydan, Shahreza, Isfahan, and Mobarakeh cities with prevalence rate of 1.58–1.89 in 1000 live birth. In 392 cases which reached to 3 years of age, the rate of TCH was 47.45%. In Chadegan, Natanz, Fereyduunshahr, Shahinshahr, Najafabad, Dehaghan, Borkhar, and Mobarakeh, the prevalence of PCH was <50%.

**CONCLUSION:** The current findings indicate that the incidence rate of both PCH and TCH are high in Isfahan province with significant variability in different cities which could be due to the role of different genetic, prenatal, and different environmental factors. These epidemiological data could be used as baseline data to design more etiological studies.

## Keywords:

Congenital hypothyroidism, permanent congenital hypothyroidism, transient congenital hypothyroidism

## Introduction

Congenital hypothyroidism (CH) is the most common endocrine disorder in neonates as well as the most common preventable cause of mental retardation in children.<sup>[1,2]</sup> CH has a worldwide incidence of 1/4000–1/3000 newborns. The incidence may be higher or lower depending on

the race, the ethnicity, and the screening method.<sup>[3]</sup> The results of the nationwide CH screening program have also indicated the high prevalence of CH in Iran.<sup>[4]</sup>

The majority of the neonates with CH are asymptomatic at birth, and delayed treatment would result in severe neurodevelopmental impairment.<sup>[5,6]</sup> Early treatment of all primarily diagnosed CH patients is crucial for their normal development.<sup>[7]</sup>

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CH is classified into two permanent and transient forms (PCH and TCH).<sup>[8]</sup> PCH mainly results from maldevelopment, absence or ectopic thyroid gland, whereas the underlying causes of transient functional impairment or TCH are less clear and may include maternal factors such as iodine deficiency, excessive iodine intake, using antithyroid medication, or the presence of antibodies against thyroid tissue during pregnancy.<sup>[4]</sup>

TCH may be caused by some factors such as iodine deficiency or excess, maternal thyroid-blocking hormone receptor antibodies, maternal use of antithyroid drugs, gene mutations such as dual oxidase 2 mutations, prematurity, and factors which affect the pituitary including medications, prematurity, and maternal untreated hyperthyroidism.<sup>[9,10]</sup> Existing data reported a higher rate of PCH and TCH in Iran including Isfahan.<sup>[11,12]</sup>

Considering the high prevalence rate of CH in Iran, it is necessary to conduct epidemiological studies in various fields to provide baseline information and insights about the etiology of the disorder and consequently for designing further interventional and preventative studies. Thus, in this study, we aimed to determine the prevalence of CH in different cities of Isfahan province. However, our findings would provide valuable information regarding potential environmental and geographical factors which could influence on the occurrence of CH.

## Materials and Methods

In this descriptive retrospective study, primarily diagnosed CH neonates who have been identified through the neonatal screening program from 2009 to 2015 and were referred to Isfahan Endocrine and Metabolism Research Center and all health centers in Isfahan for treatment and follow-up were enrolled.

All children were recalled. They were clinically examined and a pediatric endocrinologist reviewed their medical files. The medical file of each neonate consisted of three parts: demographic characteristic, CH screening, and follow-up data. Screening and follow-up laboratory data, radiologic findings, and the decision of pediatric endocrinologists regarding the final diagnosis of PCH and TCH were recorded based on medical file. In almost all cases, the diagnosis was provided by the physician (general practitioner or a pediatrician); but, in some controversial and conflicting cases, the endocrinologist made the decision. When reviewing the medical files of the neonates, the endocrinologist checked and confirmed the diagnosis. In cases with missing data, the data were completed.

## Congenital hypothyroidism screening in Isfahan

From May 2002 to April 2005, thyroxine (T4) and thyroid-stimulating hormone (TSH) serum concentrations of all 3–7-day-old newborns were measured by radioimmunoassay and immunoradiometric assay, respectively, using Kavoshyar (Iran-Tehran) kits. Thyroid function tests were performed by Berthold-LB2111 unit gamma counter equipment using serum samples. In this period, neonates with serum TSH >20 were recalled.

After implementation of nationwide CH screening program in Iran in April 2005, screening was performed using filter paper. Neonates with whole blood TSH >5 were recalled, and those with abnormal T4 and TSH levels on their second measurements (TSH >10 mIU/l and T4 <6.5 ug/dl) were diagnosed as CH patient and received treatment and regular follow-up.

Levothyroxine (LT4) was prescribed for hypothyroid neonates at a dose of 10–15ug/kg/day as soon as the diagnosis was confirmed. Neonates with CH were followed up according to the CH screening guideline for appropriate treatment regarding the level of TSH, T4, height, weight, and other supplementary tests. Monitoring of TSH and T4 was done every 1–2 months during the 1<sup>st</sup> year of life and every 1–3 months during the 2<sup>nd</sup> and 3<sup>rd</sup> years.<sup>[4]</sup>

In accordance with screening program, to provide a similar treatment and follow-up protocol, two to three workshops annually were held in different cities of the province. Cases of PCH and TCH were determined at the age of 3 years by measuring TSH and T4 concentrations 4 weeks after withdrawal of LT4 therapy. Neonates with normal TSH level (TSH < 5) were considered as TCH. Neonates with elevated TSH levels (ranged 5–10) and decreased T4 levels or TSH > 10 mIU/l were considered as PCH sufferers.<sup>[4]</sup>

## Statistical analysis

Descriptive statistics, such as mean (standard deviation) and frequency (%), was used to describe demographic and clinical parameters, variables. The Statistical Package for Social Sciences (SPSS; Release 20.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

## Results

During the period (September 2009–February 2015), 389,101 neonates were screened in Isfahan province. Of them, 47.1% were girls and 52.9% were boys.

Parental consanguinity was present among 37.3% of all screened cases. Firstdegree relative consanguinity was present among 63.5% of CH patients. Demographic and screening characteristics of the neonates are presented in Table 1.

**Table 1: Demographic and screening characteristics of screened neonates in Isfahan province (n=389, 101)**

Variable	Percent
Sex (%)	
Male	52.9
Female	47.1
Weight (g) <sup>‡</sup>	2990.65 (675.2)
Height (cm) <sup>‡</sup>	48.52 (3.76)
Head circumferences <sup>‡</sup>	34.37 (2.5)
Type of delivery (%)	
Normal	35.8
Cesarean	64.2
Maturity (>37 weeks) (%)	90.8
Nutritional status of infants (%)	
Breastfeeding	80.7
Breastfeeding + milk powder	15.5
Milk powder	3.8
Time of screening (%)	
3rd-7th days of life	81.7
After 7th day	15.3
Mean age of mother	28.06 (5.58)
First-degree parental consanguinity (%)	
1st degree	63.5
2nd degree	36.5
Mean age at treatment initiation (days) <sup>‡</sup>	24.92 (25.00)
Mean TSH level at first measurement (mIU/L) <sup>‡</sup>	42.26 (46.86)
Regular treatment and followup (%)	95.1

<sup>‡</sup>Mean (SD). TSH=Thyroid-stimulating hormone, SD=Standard deviation

Overall, 918 neonates were diagnosed as primary CH. The overall prevalence rate of CH was 2.36 in 1000 live birth (ranged 1.58–7.22 in 1000 live birth). The prevalence of CH in different cities of Isfahan province is presented in Figure 1. According to analysis in different cities, the highest prevalence rate of CH was reported in the Ardestan, Khansar, Golpaygan, and Nain cities with prevalence rate of 4.86–7.22 in 1000 live birth and lowest prevalence occurring in Fereydan, Shahreza, Isfahan and Mobarakeh cities with prevalence rate of 1.58–1.89 in 1000 live birth.

In 392 cases which reached to 3 years of age, treatment was discontinued for 4 weeks and their T4 and TSH were measured again. From which, 47.45% had TCH and remainder had PCH. The distribution of TCH and PCH in different cities of the Isfahan province are presented in Figure 2. In the following cities, the prevalence of PCH was lower than 50% and rate of TCH was high: Chadegan, Natanz, Fereyduhshahr, Shahinshahr, Najafabad, Dehaghan, Borkhar, and Mobarakeh.

According to the scintigraphic and/or ultrasonographic findings performed in 249 neonates, 90.7% had dyshormonogenesis and 9.3% had thyroid dysgenesis.

## Discussion

In this study, we reported the epidemiologic feature of CH in different cities of Isfahan province. Our result indicated that the prevalence rate of CH had a great variability in different cities of the province, and the proportion of TCH and PCH was different in the studied regions. These findings suggested that different genetic and environmental factors could influence on the incidence of CH in Isfahan province.

The main finding was that the overall prevalence of CH was high in Isfahan province. In addition, the proportion of TCH was higher in most cities of the province. Our results showed that the prevalence of CH was higher in Isfahan in comparison with other countries and also other provinces of Iran such as Fars province.<sup>[13-16]</sup>

The prevalence rate of CH had significant variability in different cities of the province ranging from 1.58 to 7.22 cases of CH cases in 1000 live birth. Observed variability could be explained by the fact that different genetic and nongenetic mainly environmental factors are in association with CH. These findings provide us new insights for designing future etiological studies in this field.

Another finding of the current epidemiological study was that the rate of TCH was higher in many cities of the province. In total population, 47.5% of the CH patients had TCH. The rate of TCH was higher than 50% in Chadegan, Natanz, Fereyduhshahr, Shahinshahr, Najafabad, Dehaghan, Borkhar, and Mobarakeh.

Based on previous reports, 17%–40% of primary CH patients are diagnosed with TCH in different newborn screening programs.<sup>[17]</sup> In our previous report from the preliminary data of CH screening program in Isfahan, from 204 patients, 40.2% of the primary diagnosed CH patients had TCH.<sup>[12]</sup>

Ordookhani *et al.* have reported a 28.6% rate of TCH for 35 neonates with primary CH.<sup>[18]</sup> In a study from Saudi Arabia, 8.3% of CH patients had TCH.<sup>[19]</sup> Gaudino *et al.* in France have reported that 38% and 62% of 79 patients with primary CH had TCH and PCH, respectively.<sup>[20]</sup> The rate of TCH was 28%, 35.2%, and 17.7% in the United States, China, and Egypt, respectively.<sup>[21-23]</sup> TCH may be due to maternal factors such as iodine deficiency, excessive iodine intake, antithyroid medication or the presence of antibodies against thyroid tissue during pregnancy, low birth weight, prematurity, immaturity of thyroidal iodine organification, exposure to excess iodine (use of iodinated disinfectants or contrast agents), and gene mutation.

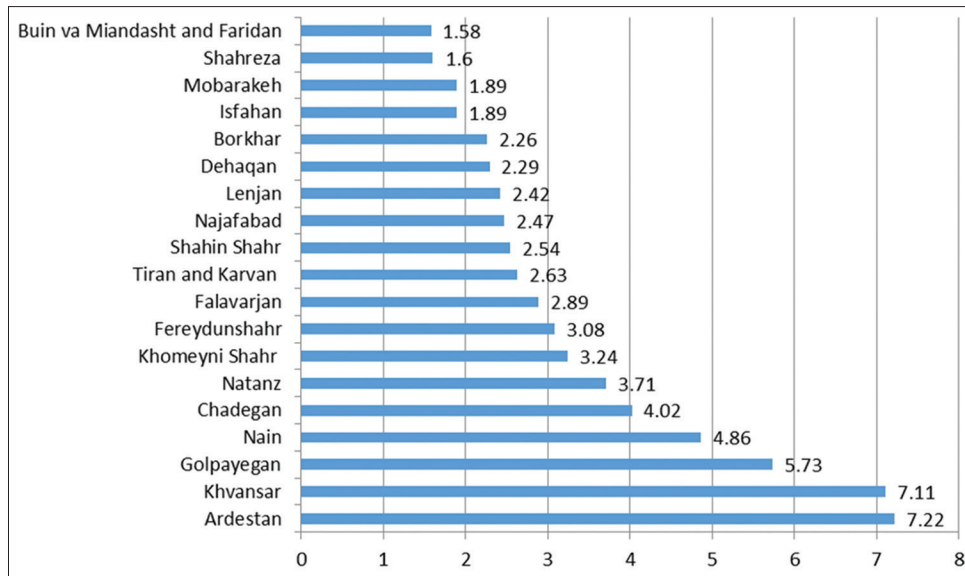


Figure 1: Prevalence (in 1000 live birth) of primary congenital hypothyroidism in different cities of Isfahan province

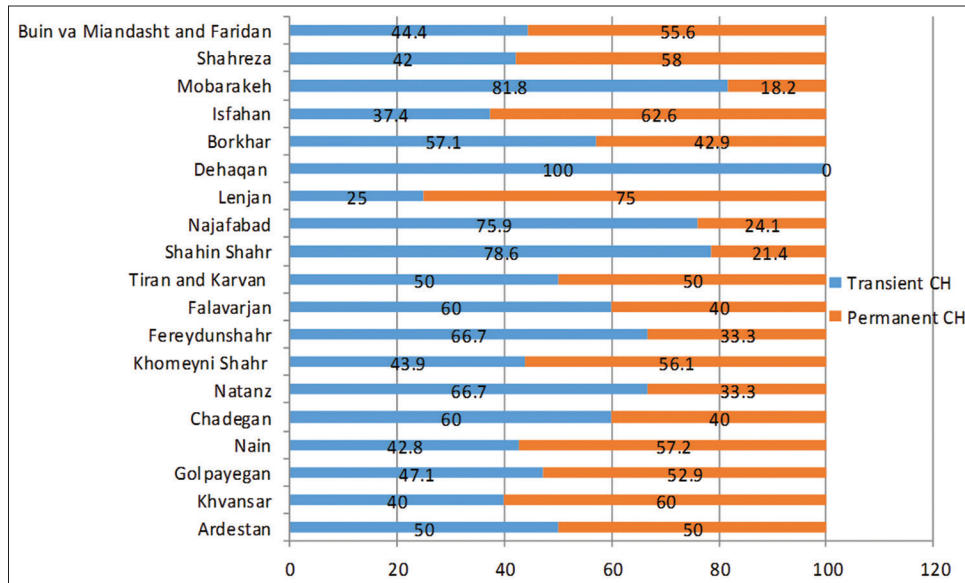


Figure 2: The distribution (%) of transient and permanent congenital hypothyroidism in neonates aged 3 years in different cities of Isfahan province

It seems that the consanguinity rate of parents and mode of delivery (cesarean section [C/S]) and some unknown environmental factors such as micronutrients deficiency or other pollutants could be the probable cause of high prevalence of CH in different cities of the province. According to some previous studies in this field, parental consanguinity may be considered as one of the main reasons for this high prevalence;<sup>[24]</sup> however, the role of other genetic, autoimmune, and environmental factors in the pathogenesis of CH should be investigated in future studies.

Our findings showed that 64.2% of neonates were delivered by C/S. Supporting our data, a recent study by McElduff *et al.* reported higher TSH levels at the 3<sup>rd</sup> day of

life in babies delivered by C/S in a large cohort of babies from thyroid screening.<sup>[25]</sup> In contrast, another study reported that the mean cord serum TSH level is higher in vaginal deliveries compared to elective C/S deliveries.<sup>[26,27]</sup> The influence of the mode of delivery on the postnatal course of serum thyroxine (T4), free T4 (f-T4), and TSH has not been well characterized. It has also been claimed that anesthetic agents given to the mother and reaching the fetal circulation through the placenta may influence the postnatal course of thyroid adaptation.<sup>[26]</sup>

The reported variability regarding the rate of TCH in different cities of Isfahan province provides us valuable data for the investigation of the causes of TCH in this region.

Regarding screening parameters, our findings showed that the mean age at treatment initiation and the rate of regular treatment and follow-up were appropriate. However, it seems that our screening program would be more appropriate if the proportion of time of screening before 7<sup>th</sup> day of life increase to more than 95%.

In the present study, we found that the mean age at treatment initiation for CH was 24.9 days. In most countries, treatment is now started earlier, usually being initiated within the first 2 weeks of life, and the accepted range for starting the treatment is considered the 45<sup>th</sup> day of life.<sup>[27]</sup> In our previous study, the mean age of treatment was  $22.9 \pm 13.2$  days of life.<sup>[24]</sup> It was also 21 days in another study in Kurdistan Province, Iran,<sup>[28]</sup> and 23 days in the screening program of Jordan.<sup>[3]</sup> These differences are the result of different screening methods. In studies using cord blood sample for screening, the mean age of starting treatment was earlier.<sup>[29]</sup>

In the current study, the consanguinity rate for parents of newborns with CH was 37.3%, and first-degree relative consanguinity was present among 63.5% of neonates with CH. Our previous study documented the high prevalence of familial marriage, especially first-degree relative consanguinity, among parents of CH neonates in Isfahan.<sup>[29]</sup> Many studies in Asian and non-Asian countries have indicated that CH is more prevalent in Asian families because of the parental consanguinity.<sup>[30]</sup>

Results of a previous study in Turkey proposed that advanced maternal age may increase the risk of mutations in genes encoding some transcription factors associated with thyroid gland development.<sup>[31]</sup> Another study indicated that advanced maternal age was more common in children with thyroid dysgenesis.<sup>[32]</sup> A study reported that children of older mothers (>39 years) had a higher incidence of CH (1:1,328) compared to younger mothers (<20 years, 1:1,703).<sup>[26]</sup> In the current study, the mean maternal age was <30 years. It seems that in our study, maternal age could not be a risk factor for the high rate of CH.

In the present study, according to the scintigraphic and/or ultrasonographic findings performed in 249 neonates, 90.7% had dyshormonogenesis and 9.3% had thyroid dysgenesis. In our previous study in Isfahan city, the prevalence of thyroid dyshormonogenesis and dysgenesis was 58.8% and 42.2%, respectively.<sup>[12]</sup> Studies from Saudi Arabia,<sup>[19]</sup> and USA,<sup>[33]</sup> also found that dyshormonogenesis was more prevalent than other etiologies. A study in Shiraz, located in the central part of Iran, indicated that the etiology of CH in 57% and 43% of cases were dyshormonogenesis and dysgenesis, respectively.<sup>[16]</sup> Parental consanguinity is considered as one of the probable causes of the high rate of thyroid

dyshormonogenesis as well as higher prevalence of CH in our region. It is expected that the prevalence of parental consanguinity is higher in dyshormonogenic CH patients than dysgenetic ones. This might be because the mode of inheritance in this group of patients is autosomal recessive, whereas in dysgenetic patients, it occurs at sporadic level with lower prevalence than other etiologies.<sup>[34]</sup>

In the current study, we reported the epidemiological findings of CH screening program in a large sample size, but our results regarding the prevalence of TCH and PCH would be more accurate if we include larger sample size of CH patients after 3 years of age.

## Conclusion

The current findings indicate that the incidence rate of both PCH and TCH are high in Isfahan province with significant variability in different cities which could be due to the role of genetic, prenatal, and different environmental factors. These epidemiological data could be used as baseline data to design more etiological studies. It would be also more favorable to use these findings to evaluate the role of some underlying factors such as micronutrients deficiency and exposure to environmental pollutants on the risk of CH in this population which were not widely evaluated.

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## Conflicts of interest

There are no conflicts of interest.

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