# Congenital Hypothyroidism in Yazd: Is It Really Prevalent?

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**Abstract-** Congenital hypothyroidism (CH) is the most frequent type of endocrine disorders which presents at birth. It plays a major role in developing the most common preventable type of mental retardation around the world. In this study, we aimed to investigate CH incidence and its predictive factors among newborns in Yazd province. This cohort study was conducted in 38 health centers of 10 cities in Yazd province which is located in the center of Iran, from March 2008 to February 2015. All neonates, as the audiences of this program, were evaluated using heel prick or *Guthrie test* according to the national protocol of CH screening. During 7 years of screening for CH from March 2008 to February 2015, 143190 neonates were screened. Among them, 434 neonates were diagnosed as affected cases by CH, and the 7-year incidence of this disease was 303/ 100,000 live births. First, cousin consanguinity, hospitalization, male sex and low birth weight had a significant relationship with congenital hypothyroidism. Logistic regression analysis revealed that aforementioned variables in addition to delivery type (cesarean section) were significant predictor of CH. CH is more prevalent in Yazd compared to the other provinces in Iran. It is recommended that the effects of probable risk factors are evaluated through additional longitudinal studies and effective preventive strategies are designed according to the results.



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**Keywords:** Congenital hypothyroidism; Incidence; Risk factors

## Introduction

Congenital hypothyroidism (CH) is the most frequent type of endocrine disorders that present at birth with the incidence of nearly one in 2500 live neonates (1). The importance of this disease is attributed to this fact that it plays a major role in developing the most common preventable type of mental retardation around the world. Most of the children with CH have no apparent symptoms or signs at early months after birth, but the continuity of thyroid hormone deficiency leaves negative impacts on brain development which gradually leads to mental retardation (2). However, the presence of thyroid hormone deficiency in affected newborns can be diagnosed through simple laboratory tests. These characteristics bring the disease into the spotlight and signalize the need for universal screening programs. In this regard, *Dussault* and colleagues established CH screening for the first time in Quebec, Canada in 1974 (3). After that, most developed and some underdeveloped countries continued this way and implemented this screening program for newborns (4).

Azizi and collogues started to screen CH among neonates in Iran for the first time in 1987 (5) and the program, as a universal practice, entered officially to health care programs in 2005 (6). Since that date, all neonates borne in Iran have been the audiences of this program, and more than 92 % have been screened through that (7). The pooled incidence derived from the results of national program has revealed higher CH incidence in Iran (200:100000) (6) compared to some parts of the world (8,9). Meanwhile, reports from different provinces of Iran demonstrated heterogeneous pattern for the prevalence (10).

In addition to above, there is some evidence that multiple risk factors such as sex, birth weight, parental consanguinity and maternal age impress the incidence of CH (11). It seems that identification of such risk factors and their relationship with disease incidence and employing them in diagnosis process make earlier recognition and management more possible for clinicians. Therefore, in this study, we aimed to

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investigate CH incidence and its predictive factors among newborns in Yazd province.

## Materials and Methods

This cohort study was conducted in 38 health centers of 10 cities in Yazd province which is located in the center of Iran, from March 2008 to February 2015. All neonates, as the audiences of this program, were evaluated using heel prick or *Guthrie test* according to the national protocol of CH screening. In this regard, 3-4 blood drops were captured from the heels of newborns using special auto-lancets, collected on *Whatman 903* filter paper and dried in the room temperature. Dried specimens were transported to provincial reference laboratory with express mail within 24 hours, and in all of them, TSH level was evaluated using ELISA test. TSH level less than 5 among 3-7 day newborns and less than 4 among neonates who were more than 7 days old were considered to be normal. In the case of prematurity; LBW; some medical treatments including Amiodaron, Dopamine, and corticosteroids; hospitalization; blood transfusion or exchange and multiple pregnancy screening tests was repeated in second weeks after birth. For neonates in whom TSH level was detected to be higher than aforementioned cut points; venous blood sample was taken in order to measure T4, TSH, and T3RU. Time of taking blood sample was determined according to the level of TSH as newborns with TSH 5-9.9 in the $4^{th}$ week and those with TSH 10-19.9 in $2^{nd}$ -$3^{rd}$ week were assessed and neonates who had TSH level of 20 and more had to be evaluated as soon as possible. When T4 <6.5 µg/dl and TSH >10 were detected in newborns, CH diagnosis was established for them.

**Statistical analysis**

All available data including sex, hospitalization, LBW, macrosomia, delivery type, residence, prematurity, multiple pregnancy, birth season, parental consanguinity and maternal age were recorded and analyzed in SPSS version 22 (IBM 22). Associations between these variables and CH incidence were evaluated through univariate analysis including independent sample T-test for maternal age and *Chi*-squared test for the others. In addition, logistic regression method was employed to assess the effect of independent variables on CH occurrence. In this regard, variables which had gained $P<0.2$ in univariate analysis were included in the logistic regression. In other situations, $P<0.05$ was considered to be significant.

## Results

During 7 years of screening for congenital hypothyroidism from March 2008 to February 2015, 143190 neonates were screened. Among them, 434 neonates were diagnosed as affected cases by CH, and the 7-year incidence of this disease was 303/100,000 live births. Characteristics of neonates have been shown in table 1.

**Table 1. Neonates' characteristics**

| Variables | Category | Frequency (%) or Mean(SD) |
|---|---|---|
| **Gender** | **Female** | 69758 (48.7) |
| | **Male** | 72053 (50.3) |
| **Residence** | **Urban** | 131212 (91.6) |
| | **Rural** | 11899 (8.3) |
| **Parent relativeness** | **First cousin** | 24607 (17.2) |
| | **Second cousin** | 13446 (9.4) |
| | **Nonrelative** | 103574 (72.3) |
| **Maternal age (year)** | | 26.77 (5.1) |
| **Season of birth** | **Spring** | 33286 (23.2) |
| | **Summer** | 38573 (26.9) |
| | **Autumn** | 36024 (25.2) |
| | **Winter** | 35307 (24.7) |
| **Delivery type** | **Vaginal delivery** | 73074 (51) |
| | **Cesarean section** | 68555 (47.9) |
| **Weight (gr)** | | 3122.12 (26.7) |
| **LBW** | **Yes** | 7609 (5.3) |
| **Macrosomia** | **Yes** | 2655 (1.9) |
| **Twin** | **Yes** | 2791 (1.9) |
| **Hospitalization** | **Yes** | 5969 (4.2) |
| **Prematurity** | **Yes** | 813 (0.6) |

Most of the neonates (92.8%) underwent screening test on the 3rd-7th day after delivery, and the rest were evaluated after the 7th day of birth. According to the results of TSH level assessment, 97.2% of neonates had TSH level less than 5 (normal level). In the rest of neonates, 2.7% had TSH 5-9.9, and 0.1% had TSH 10 and more. Totally, 3915 neonates (2.73%) were recalled for more evaluation after the first test (recall rate).

In current study, parental consanguinity was significantly much more prevalent among neonates affected by CH in comparison with non-affected neonates, as the disease was occurred in 0.4% of neonates of parents with the first-cousin consanguinity, 0.31% of neonates of parents with second-cousin consanguinity and 0.2 % of neonates of non-relative parents (*P*=0.008).

In the present study, neonates who had been hospitalized during the first days of birth were more affected by CH than the others (0.79% vs. 0.28%, *P*<0.001). In addition, male neonates were more affected by the disease than females (0.3% vs. 0.2%, *P*:0.001). Moreover, there was a significant relationship between low birth weight (LBW) and CH (*P*<0.001). In detail, 0.63% of neonates with LBW versus 0.28% of neonates with normal birth weight had diagnosed with CH.

Other probable risk factors including area of residence (urban/rural), birth season, maternal age, macrosomia, prematurity and multiple pregnancies had no significant relationship with CH.

Logistic regression analysis was applied to some aforementioned variables including sex, hospitalization, LBW, delivery type, prematurity, multiple pregnancy, season and parental consanguinity and finally sex, hospitalization, LBW, consanguinity (first-cousin) and delivery type (C/S)remained significant in the model and were considered as predictors of CH occurrence (Table 2).

**Table 2. Predictor variables of CH incidence derived from logistic regression model**

| Variables | | OR | CI | *P* |
|---|---|---|---|---|
| **Sex** | **Male** | 1.41 | 1.16 - 1.72 | < 0.001 |
| **Hospitalization** | | 2.45 | 1.78 – 3.37 | < 0.001 |
| **LBW** | | 2.17 | 1.60 – 2.95 | < 0.001 |
| **Delivery type** | **C/S** | 0.81 | 0.66 - 0.97 | 0.035 |
| **Prematurity** | | 0.70 | 0.25 - 1.94 | 0.494 |
| **Multiple pregnancies** | | 1.04 | 0.57 – 1.88 | 0.892 |
| **Season** | **Spring** | 1 | | |
| | **Summer** | 0.85 | 0.64 - 1.13 | 0.280 |
| | **Autumn** | 0.96 | 0.72 – 1.27 | 0.786 |
| | **Winter** | 1.12 | 0.86 – 1.47 | 0.381 |
| **Parental consanguinity** | **Non-relative** | 1 | | |
| | **Third degree** | 1.37 | 1.08 – 1.73 | 0.008 |
| | **Forth degree** | 1.08 | 0.78 - 1.51 | 0.609 |

## Discussion

In the present study, the 7-year incidence of CH has estimated about 303 in 100,000 live births. It is while 42.2 out of 100,000 American neonates suffered from CH in 2002(12). In addition, CH affected 70 in 100,000 Italian neonates during 7 years of follow up from 1999 to 2005 (13). Therefore the incidence of CH in our province is estimated to be up to 7 times more than some other countries.

Looking at the studies conducted in Iran revealed that the incidence of the disease reported 325, 270 and 150 in 100,000 in Markazi (10), Isfahan (14) and East Azerbaijan (15) respectively. Moreover, Fars beard a burden of 68 affected neonates in every 100,000 live births in 2011 (16). According to a meta-analysis conducted on Iranian studies in 2014, pooled prevalence of CH was reported to be 200:100,000. While the CH prevalence in Iran is estimated to be high in comparison with other countries, there is significant variability between different provinces, and it seems Yazd is placed amongst high-prevalence provinces in Iran.

Although the underlying reasons for these variations are not clear, several promoting factors can be assumed. One of the underlying reasons might be the usage of different screening protocols. There is no unique international protocol for CH screening, and different methods are available around the world including TSH measurement at baseline following T4 measurement backup, T4 measurement at baseline following TSH measurement and simultaneous TSH and T4 measurement (17). Moreover, the selected cut points for

CH diagnosis have been different in various studies. For example, according to the screening protocol used in Greece, neonates with first TSH more than 20 were considered to be suspected case and candidate for further evaluation (18). In Egypt, if the TSH level had been demonstrated to be >=15 in a neonate, he/ she would have need complementary assessment to confirm the diagnosis of CH (19). In Turkey, TSH cut point had been set on 20 µU/ml previously and then it was changed to 15 µU/ml in recent years (9). The above explanation can be considered as a justification for observed different incidence between countries. However, the CH screening program started from2005 in Iran (6) has followed a relatively uniform protocol with minimal change, from the beginning up to now. According to Iranian screening program, neonates with TSH level of 5 and more are candidate for more assessment. Therefore, other causes than various protocols and cut points may play a determinative role in diverse prevalence among provinces and also higher CH occurrence in Iran.

Iodine deficiency is one of the most important risk factors for CH occurrence. Although there is no published recent study on the iodine status in Iran, one comprehensive study demonstrated that not only there has been no iodine insufficiency, but "more than adequacy" status can be considered for this country (20). However, the studies in the United States of America have demonstrated that nearly 15% of women in reproductive age range suffer from iodine deficiency despite the whole population that has sufficient iodine level (21). These results enhance this hypothesis in mind that iodine deficiency can be one of the problems during pregnancy in Iran and therefore further updated iodine level assessment should be performed especially among pregnant women.

Some studies proposed Asian race as another suspected risk factor. What attracts attention to Asian people is high level of consanguinity marriage among them. Therefore, scientists put consanguinity marriage under consideration as a probable risk factor. The results of related studies illustrated that CH is much prevalent among neonates from consanguineous (22) especially first-cousin parents than the others (14). The current study also revealed that having third-degree relative parents can make neonates 1.37 folds much more susceptible to CH than having nonrelative parents. Therefore, parental consanguinity can be assumed as one of the predisposing factors of CH among neonates.

According to the findings of the present study, hospitalization was the most important risk factor for CH, as neonates with the history of hospitalization had 2.5 folds more chance to be affected by CH than the others. The explanation may be that hospitalized neonates receive various medical treatments and some of them should undergo blood exchange. These interventions can impress hormonal status of these neonates including TSH (23).

Our study findings, in line with some other studies (11,24), demonstrated that Low birth weight (LBW) is a contributing factor to CH occurrence. In detail, neonates with birth weight less than 2500 gr had two folds higher risk to be afflicted with CH in comparison with other neonates. On the other hand, according to the current protocol of screening in Iran, neonates with LBW should be reevaluated by heel prick blood test if the first TSH result falls within normal range. This recommendation is due to this finding that "delayed TSH elevation" has been demonstrated to be a common finding among neonates who have been born with birth weight less than 2500 grams (25,26). Therefore, it is strongly recommended that LBW does remain as a factor to repeat TSH measurement after the initial normal value.

Another finding of our study illustrated that neonatal gender might have a significant impact on CH incidence. In detail, CH had occurred in higher frequency among male compared to female neonates. This finding was in line with some but completely different from most studies which evaluated the aforementioned relationship and illustrated that being female might increase the risk of the disease (27,28). According to the literature, female neonates suffer from CH more than male neonates, but the feature of the disease appears to be more severe among males (29). There is no clear scientific justification for this finding in the literature and further studies are needed to evaluate the importance of gender in the CH development.

Surprisingly, the results of the current study demonstrated that cesarean section played a protective role in CH occurrence. It means vaginal delivery increased the risk of disease incidence in neonates. The reason for this finding is not clear, but it is believed that stressful events associated with vaginal delivery can affect TSH level and make it be higher in neonates born by this method (30,31).

According to the findings of the present study, CH is more prevalent in Yazd compared to the other provinces in Iran. Some variables including first cousin consanguinity, hospitalization, male sex and low birth weight had a significant relationship with congenital hypothyroidism. Moreover, logistic regression analysis revealed that aforementioned variables in addition to

delivery type (cesarean section) were significant predictors of CH incidence. As the results demonstrated that some risk factors are modifiable or preventable, it is recommended that the effect of these and other probable risk factors are evaluated through additional longitudinal studies, and effective preventive strategies are designed according to the results.

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