Original Article

Congenital Hypothyroidism and its Related Factors in an Iranian Population: A Retrospective Study in Semnan (2011–2016)

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Abstract

Background: Congenital hypothyroidism (CH) is an important and preventable cause of intellectual disability. This study determined the incidence of CH and its related factors in Semnan city in Iran. **Methods:** All neonates born in Semnan from 2011 to 2016 who participated in a screening program for CH were evaluated to estimate the incidence of CH. In a nested case-control study, all diagnosed CH cases were compared with a control group of healthy newborns. Statistical analysis used conditional logistic regression model with STATA-14. **Results:** 106 out of 17,507 neonates born in Semnan during 2011–2016 were diagnosed with CH (6.05 cases per 1,000 live births). Maternal parity (odds ratio [OR] =1.78, P = 0.044), birth weight (OR = 0.29, P = 0.001), parental history of thyroid disease (OR = 3.43, P = 0.001), father's education (OR = 0.71, P = 0.003), father's occupation (nonworker) (OR = 2.97, P = 0.001), and the presence of other anomalies (OR = 4.14, P = 0.037) were related to the incidence of CH. **Conclusions:** The cumulative incidence of CH in Semnan was higher than in both the global and national statistics. Aside from well-known medical determinants, some important social factors such as father's occupation and education have a significant and independent relationship with occurrence of CH; rational attention should be given to them in health care programs to increase the effectiveness of preventative measures for CH.

Keywords: *Congenital hypothyroidism, incidence, Iran, risk factors*

Introduction

Congenital hypothyroidism (CH) is the most common endocrine disorder in newborns and the most usual and preventable cause of intellectual disability.[1,2] Patients with CH also suffer from intellectual disability (ID) because of the pivotal role of the thyroid hormone in the development and growth of the brain.[3] Studies carried out on the follow-up of these patients show that delays in the diagnosis and treatment of this disease may be accompanied by known neurological complications such as ID, and other complications such as motor disorder, imbalance, learning difficulties, failure to thrive, and permanent short stature, which can be prevented with early diagnosis and timely treatment.[4] The intelligence quotient of the newborns with CH may remain at a normal level through early diagnosis and timely treatment.[5]

Scientific information shows that about one-third of maternal thyroxine (T4) is transmitted to the fetus through the umbilical cord; this amount of T4 is responsible for preventing major clinical symptoms in the fetus.[6] Many newborns with CH have a normal appearance and clinical symptoms are minor and nonspecific at birth, and only less than 5% of newborns are diagnosed with clinical symptoms.[3,5] Considering that it is necessary to start treatment with thyroid hormone before the 6th week of life to prevent irreversible complications of hypothyroidism, it is only possible to diagnose CH early and prevent intelligence quotient decline through screening infants in the first days of life.[5,7,8]

Studies on hypothyroidism screening started in North America in 1972.[9] In Iran, Azizi *et al*. carried out screening programs for hypothyroidism in 1987 for the first time.[3,7,10] The prevalence of CH is 1 per 3,000–4,000 newborn-years.[11] A study conducted in New York reported the prevalence of CH is higher in the Asian race and, according to the CH screening report; CH is more prevalent in Iran (1–2.7 per 1,000 live births).[12-14]

Inadequate iodine in the diet is the most common cause of CH worldwide. The WHO Regional Office for the Eastern

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Mediterranean has declared Iran has enough iodine in the diet since 1996. The role of iodine deficiency as the cause of the high rate of hypothyroidism is less emphasized, and other issues such as race, sex, twinship, and genetics are introduced as risk factors for CH.[5,6,15,16]

Because of the relatively high prevalence of this disease in Iran and its importance in ID, factors associated with CH in the population of Semnan were investigated during 2011–2016.

Methods

This study was conducted in two stages. The first stage was a cross-sectional study of the health records of all newborn infants born in Semnan during 2011–2016, who participated in the thyroid screening program to estimate the cumulative incidence of CH. According to the screening protocol, thyroid-stimulating hormone (TSH) values higher than 5 mu/L in blood from a heel prick from 3 to 7-day-old newborns after confirmatory venous TSH sample higher than 10 mu/L and T4 lower than 6.5 μg/dL was used as a diagnostic criterion for CH. In the second stage, a nested case-control study was performed. All newborns with CH participated as the case group. Two healthy newborns were selected randomly per each newborn with CH from the same center as control group (the date of birth of the newborns selected as control participants was the same as the date of birth of the newborns selected as case participants). Data of these newborns were extracted from records stored at www.sib.sbmu.ac.ir (an internet page for storing electronic health records). The data included birth month and year, sex of the newborn, gestational age, twinship, birth weight, birth length, newborn's head circumference, presence of other anomalies in the newborns, maternal parity, type of childbirth, maternal age, maternal BMI before the pregnancy, cousin marriage, parental occupation and education, and parental history of thyroid diseases.

To estimate the overall and annual cumulative incidence, the ratio of newborns with CH to the total births was calculated as "per 1,000 births." Frequency distribution tables described the findings. To illustrate the relationship between any factors of interest with hypothyroidism in newborns, crude and adjusted odds ratio (OR) were calculated as point and interval estimations with 95% confidence interval through simple and multiple conditional logistic regression models using STATA-14 software. The interpretation was based on the final reduced model extracted by backward method using likelihood ratio test. A *P* value less than 0.05 was considered significant.

Results

In this study, the average incidence of CH was estimated to be 6.05 per 1,000 live births; therefore, the estimated annual incidence was calculated as 1.80 to 8.87 per 1,000 live births during 2011–2016. Table 1 shows the number of births and cases with CH in Semnan by year.

Table 1: Cumulative incidence of congenital hypothyroidism in Semnan (2011–2016)

Year	Total births	Cases	Incidence*
2011	2778	5	1.80
2012	2913	10	3.43
2013	2877	18	6.26
2014	2927	26	8.88
2015	3043	27	8.87
2016	2969	20	6.74
2011-2016	17507	106	6.05

*per 1,000 births

In the case group, 61 (1.58%) newborns were male and 44 (9.41%) newborns were female and in the control group, 98 (7.46%) newborns were male and 112 (3.53%) newborns were female. In the case group, 7.6% of the gestational age was 32 weeks and less, and 9.2% of the gestational age was between 32 weeks and 34 weeks; in the control group, no gestational age was 32 weeks or less, and only 1% was ranged from 32 weeks to 34 weeks. The gestational age of 3.73% of newborns with CH was higher than 37 weeks, and in the control group, 89% of gestational age was higher than 37 weeks. Table 2 shows the frequency distribution of the specifications of the newborns of both case and control groups.

Table 3 shows the crude and adjusted ORs of each of the studied characteristics and factors of CH based on simple, multiple, and final reduced models. The simple logistic regression models and based on estimating crude OR shows gestational age and birth weight were two factors associated with the increased odds of CH; maternal parity, history of thyroid disease in at least one parent, anomaly, and twinship were the factors associated with the increased odds of CH. In the multiple regression model, gestational age, presence of anomalies, and twinship were not significant, while father's occupation (nonworker) was significant as a factor increasing the odds of CH. In the reduced final model, there was a significant relationship among six factors of maternal parity (OR = 1.78, $P = 0.044$), birth weight (OR = 0.29, $P = 0.044$), parental history of thyroid diseases (OR = 3.43, $P = 0.001$), paternal education (OR = 2.97, $P = 0.001$), father's occupation (OR = 2.97, $P = 0.001$), and the presence of other anomalies (OR = 4.14, $P = 0.037$) and CH.

The results of this study do not show a significant relationship among the other variables including maternal age at the time of childbirth, maternal BMI before pregnancy, cousin marriage, type of childbirth, and the length and head circumference of the newborn at birth, and CH.

Discussion

Considering the definition of CH in this study, hypothyroidism diagnosis is merely based on newborn birth's primary screening and children follow-up were

Table 2: Characteristics of newborns separated by case and control groups

Characteristics		Percentage (count)	
		Control group	Case group
Sex	Male	46.7% (98)	58.1% (61)
	Female	53.3% (112)	41.9% (44)
Gestational age (week)	≤37	11.0% (23)	26.7% (28)
	>37	89.0% (187)	73.3% (77)
Maternal age (year)	≤35	87.1% (183)	89.5% (94)
	>35	12.9% (27)	10.5% (11)
Maternal BMI (kg/m²)	≤18	4.8% (10)	1.9% (2)
	18–35	91.4% (192)	95.2% (100)
	>35	3.8% (8)	2.9% (3)
Maternal parity	First pregnancy	49.0% (103)	35.2% (37)
	Not first pregnancy	51.0% (107)	64.8% (68)
Cousin marriage	Yes	31.0% (65)	36.2% (38)
	No	69.0% (145)	63.8% (67)
Delivery type	Vaginal	41.0% (86)	34.3% (36)
	Cesarean	59.0% (124)	65.7% (69)
Birth weight (g)	≤1000	0.0%(0)	2.9% (3)
	>1000–4000	96.2% (202)	95.2% (100)
	>4000	3.8% (8)	1.9% (2)
Father's education	Nonacademic	65.7% (138)	77.1% (81)
	Academic	34.3% (72)	22.9% (24)
Mother's education	Nonacademic	61.9% (130)	67.6% (71)
	Academic	38.1% (80)	32.4% (34)
Father's occupation	Worker	45.7% (96)	36.2% (38)
	Nonworker	54.3% (114)	63.8% (67)
Mother's occupation	Housewife	85.2% (179)	85.7% (90)
	Employed	14.8% (31)	14.3% (15)
Birth length (percentile)	<25th	3.8% (8)	3.8% (4)
	25th–75th	82.4% (173)	84.8% (89)
	>75th	13.8% (29)	11.4% (12)
Head circumference	Normal	98.1% (206)	96.2% (101)
	Abnormal*	1.9% (4)	3.8% (4)
Thyroid disease in mother	Yes	91.0% (191)	84.8% (89)
	No	9.0% (19)	15.2% (16)
Thyroid disease in father	Yes	91.0% (191)	78.1% (82)
	No	9.0% (19)	21.9% (23)
Congenital anomalies	Yes	98.1% (206)	93.3% (98)
	No	1.9% (4)	6.7% (7)
Twin ship	Yes	97.1% (204)	91.4% (96)
	No	2.9% (6)	8.6% (9)

*Microcephalic or macrocephalic, BMI=Body mass index

not conducted, transient and permanent hypothyroidism cannot be distinguished and therefore general term CH is employed.

Although the incidence of CH varies from one region to another, it is generally estimated to be 1 per 3,000–4,000 live births worldwide, and recent studies have shown an increasing trend.[6-18] In a study conducted by Olivier *et al*. in Italy in 2015, the incidence of CH had increased from a ratio of 1 to 3,000 to a ratio of 1 to 1,940 live births during the period 1987–1998 (period 1) and the period 1999–2008 (period 2).[19] In an investigation carried out by Deng *et al*. in 2018, the incidence of CH was reported to be 4.13 cases per 10,000 live births in China.[20] In a study performed by Alenazi *et al*. in 2017, the prevalence of CH was reported to be 2.6 per 10,000 live births in the north of Saudi Arabia.[21] A variation in the ethnicity-specific incidence of CH has been reported in previous studies.[18,22,23] Differences are more likely due to iodine deficiency thyroid disorders or to the type of screening method than to ethnicity.[24]

Table 3: Crude and adjusted odds ratios of each studied factors with congenital hypothyroidism based on simple, multiple, and final reduced models

Factor	Initial simple model		Multiple model		Final reduced model	
	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Sex (female)	0.63 (0.39-1.01)	0.057	0.67 (0.38-1.16)	0.152	0.63 (0.37-1.08)	0.094
Gestational age	0.39 (0.25-0.62)	0.001	0.98 (0.45-2.10)	0.962	-	-
Maternal age	1.04 (0.84-1.30)	0.68	0.94 (0.70-1.26)	0.711	-	-
Maternal BMI	0.93 (0.72-1.21)	0.633	0.87 (0.64-1.20)	0.419	-	-
Maternal parity	1.76 (1.09-2.86)	0.021	2.03 (1.04-3.97)	0.037	1.78 (1.01-3.13)	0.044
Cousin marriage	1.26 (0.77-2.07)	0.351	1.14 (0.63-2.05)	0.661	-	-
Delivery type (cesarean)	1.32 (0.81-2.16)	0.253	0.99 (0.55-1.76)	0.977	-	-
Birth weight	0.35 (0.21-0.58)	0.001	0.30 (0.14-0.64)	0.002	0.29 (0.16-0.51)	0.001
Father's education	0.87 (0.74-1.03)	0.110	0.77 (0.57-1.03)	0.082	0.71 (0.58-0.89)	0.003
Mother's education	0.91 (0.79-1.05)	0.232	0.88 (0.67-1.16)	0.397	-	-
Father's occupation (non-worker)	1.54 (0.95-2.51)	0.077	3.23 (1.66-6.27)	0.001	2.97 (1.57-5.64)	0.001
Mother's occupation (Employed)	0.96 (0.49-1.87)	0.910	1.42 (0.59-3.43)	0.427	-	-
Birth length	0.86 (0.47-1.55)	0.618	1.11 (0.54-2.25)	0.771	-	-
Newborn's head circumference	0.69 (0.16-2.94)	0.617	3.13 (0.59-16.45)	0.177	-	-
Parental thyroid diseases	2.82 (1.45-5.45)	0.02	3.37 (1.56-7.29)	0.002	3.43 (1.63-7.20)	0.001
Anomaly	3.67 (1.05-12.86)	0.041	3.81 (0.95-15.25)	0.059	4.14 (1.09-15.71)	0.037
Twin ship	3.18 (1.10-9.21)	0.032	1.62 (0.39-6.77)	0.502	-	-

CI=Confidence interval, OR=Odds ratio, BMI=Body mass index

Sporadic studies conducted in regions and provinces in Iran reported the incidence of CH to be 1 per 60 live births in Shadegan,[25] 1 per 491 in the northern Iran,[26] 1–1.6 per 1,000 in Mazandaran province,[3] 1 per 549 in South Khorasan province,[12] 3–5.2 per 1,000 live births in Sanandaj,[5] and in a study in 2016 in Yazd province, the incidence of CH was reported to be 3.4 cases per 1,000 live births.[8] In research done by Mehdi Osouli *et al*. in 2008, the overall incidence of CH in Iran was estimated to be 2.2 cases per 1,000 live births.[27]

According to the results of our study, the incidence of CH was 1.80 in 2011 to 6.74 in 2016 per 1,000 live births. The overall trend in incidence has increased over these years. Since the present study was a retrospective research and some information concerning on environmental factors such as maternal and neonatal iodine concentration and genetic factors such as the presence of thyroid receptor inhibitor antibody are not available, a precise explanation for this variation might not be possible; however, it can be largely explained by the increased coverage and effectiveness in the screening program over time. Considering its cumulative incidence over the years, estimated as 6.05 per 1,000 live births, the incidence is much higher than the overall incidence of CH in Iran.

In our study, the relationship among 17 factors with CH was examined [Table 3]. The results show a statistically significant relationship among the variables of maternal parity, birth weight, parental history of thyroid disease, father's education and occupation, and other anomalies with CH. Some studies conducted to examine the risk factors for CH introduced female sex as a risk factor.[8,21] For example, in a study by Yang *et al*., female sex was introduced as a risk factor for CH.[21] In Iran, although there was no significant relationship between sex and CH in the studies performed by Namakin *et al*. and Keshavarzian *et al*., the number of male newborns with CH were higher; the results of the present study is in line with these results in Iran.[12,25]

In the present study, data show a significant relationship between maternal parity and CH, and the odds of the CH was higher when the mother had more pregnancies. Similar to the results of the present study, the study carried out by Razavi *et al*. showed a significant relationship between the CH and the number of pregnancies.[28]

In our study, at least one parent of 21.9% of newborns with CH had a history of thyroid disease, and there was a statistically significant difference between the case and control groups. When one or both parents have a history of thyroid disease, the odds of the CH is higher in newborns. The results of the study performed by Abedi *et al*. indicated a significant relationship between family history of thyroid diseases and occurrence of CH.[5] However, multivariate analysis in the study of Esmaeil Nasab *et al*. showed no significant relationship between family history of thyroid disease and CH in newborns.[1]

Other findings of the present study showed a significant association between birth weight and CH. The odds of CH was lower in neonates with higher birth weight; however, the relationship was not statistically significant among birth length and newborn's head circumference and CH. The results of Dalili *et al*.'s study showed both low and high birth weight (including macrosomia) were risk factors for CH.[11] Shojaeifar *et al*.'s study showed a significant relationship between higher incidence of CH in newborns

with a birth weight below 2,500 g compared with a birth weight of 2,500 g or more.[8] In their study on factors associated with CH, Rezaeian *et al*. showed statistically higher odds of the incidence of CH in neonates with birth weight lower than 3,500 g than in the control group.[14] According to the results of the present study, in which infants with low birth weight had a higher risk of CH, it may be partly attributable to the higher risk of iodine deficiency in low birth weight infants.

In the present study, the odds of the incidence of CH in newborns with anomalies were higher. In Razavi *et al*.'s study, a significant relationship was also observed between congenital anomalies and CH.[28]

Two specifications of the father's education level and his occupation as a worker had a preventative role in occurrence of CH. As the most social determinants of health, education, and occupation can influence both risk factors and health-related consequences directly or indirectly. CH is no exception. Nevertheless, due to inevitable social, cultural, and geographical complications and interactions, extracting pure impact of social factors in a study is an arduous task; hence, justifying the inconsistency of previous studies regarding this mater. According to the results of the present study; with father's education status promotion, the incidence probability displayed significant decreased. To further elucidate this finding, it can be declared that the higher socioeconomic level associated with parents' education, especially fathers, maybe pertinent with higher levels of preventive or health care and services, as well as better nutrition status. On the other hand, since parental awareness pertaining thyroid disorders, consumption method or anti-thyroid or hypothyroidism medications' dosage or type alterations, supplement administration (including iodine-containing supplements), prepregnancy, pregnancy, and postpartum maternal and childcare can all be related to the level of parental health knowledge and their education level, this led us to consider this element, so that through promoting families' health status and training parents with sufficient materials, occurrence of a serious congenital disorder in the neonate can be prevented at least by eliminating a simple environmental factor.

In respect to occupation, it should be declared that our perspective toward job classification in the article's analysis was more of an epidemiologic view rather than an etiologic one. In fact, we strived to consider the job variable as an underlying or major confounding factor. According our findings, it was revealed that the chance of incidence in newborns with a proletarian father was less. Regarding this matter, this finding can relate to the well-known influence of the "Healthy Worker Effect" to some extent, which implies that proletarians are healthier than public which is conceivable in the current study as well. Workers are in better health conditions because they must fulfill rigorous recruitment criteria when they want to begin their jobs and they are continuously monitored, and also they receive more accurate health care after recruitment.

Limitations in the sample size due to the relatively small population of the region as well as the examination of other variables and background specifications due to the retrospective nature of the study and reference to the records registered in the current health system are the issues that should be considered when interpreting the results. To reduce the effect of the relatively small sample size on the ability to analyze, two control participants were selected and participated in the study per each case participant. On the second limitation, we suggest and recommend population-based futures studies in Iran.

Conclusions

In this study, the cumulative incidence of CH in Semnan was higher compared with global and national statistics. Aside from medical factors and parameters such as maternal parity, birth weight, parental history of thyroid diseases, and the presence of other anomalies in the newborn, two important social factors—father's occupation and education—have a significant and independent relationship with this disease. We suggest giving attention to these underlying factors in health care programs for pregnant women in order to increase the effectiveness of preventative measures for CH.

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Conflicts of interest

There are no conflicts of interest.

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