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Original Article

Investigation of risk factors associated to congenital hypothyroidism in Mahshahr city between 1389-1395 and presentation of a preventive model

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ABSTRACT

Background and Objectives: Congenital hypothyroidism is one of the important factors of mental retardation and neonatal prevention. The aim of this study was to evaluate the risk factors associated with congenital hypothyroidism and introducing a preventive model. Materials and Methods: By a case-control study all newborns suffering from congenital hypothyroidism who were identified through a screening program during 1389-1395, were selected as the case group and for each case, a healthy neonate born at the same date and the same area was selected as the control. The required information was collected by a questionnaire and entered into SPSS version 20. Data were analyzed using T test, Chi-square, Fisher exact test and logistic regression and then the results of the logistic regression model were compared with discriminant function model. The p value equal or less than 0.05 was considered as significance level in all tests. Findings: Totally 104 neonates with congenital hypothyroidism and the same number among healthy infants were enrolled in the study during 1389 – 1395. Among control group, 52% were female (54 neonates) and 48% were male (50 neonates) and among case group, 43.3% (45 neonates) were female and 56.7% (59 neonates) were male. The mean ± SD of weight for the case group was 2995. 385 ± 613.1 grams and for the control group was 3176. 731 ± 490.2 grams with a significant difference (p = 0.019). This study showed that the chance of having a congenital hypothyroidism at a gestational age ≤37 weeks was 8.8 times more than gestational age >37 weeks (OR = 6.8; 95%CI:71.3-89%, P = 0.049). Also, the chance of having congenital hypothyroidism among newborns with a positive history of hypothyroidism in the family was 3.03 times more than those with a negative history (OR = 3.03; 95%CI: 0.13-9.8%, P = 0.043). There was no a significant relationship between other environmental, familial and medical factors with the risk of congenital hypothyroidism. Also, the diagnostic function model showed that using the variables of fetal age below 37 weeks, the birth weight of infants and the existence of a positive familial history of thyroid disease can predict the congenital hypothyroidism in the baby with a specificity and sensitivity of 85.6% and 33.7% respectively. Conclusion: The study showed that the history of thyroid disease in the family, the gestational age and the weight of baby at birth are factors associated with congenital hypothyroidism. Considering the related factors, a preventive model was presented for congenital hypothyroidism.

Keywords: Congenital hypothyroidism, neonates, risk factors, prevention model

Introduction

Maternal retardation is a condition in which due to thyroid hormone defects or low thyroid hormone biosynthesis, thyroid hormone concentrations are low in the baby's bloodstream. This is one of the most commonly reported causes of mental retardation [1]. The hippo thalamus axis begins to function in the middle of the fetal period and develops until the term begins. If there is a hypothyroidism in the fetus, disturbances in an important organ, including the central nervous system and skeletal system, are created. The irreparable brain damage and longevity of these lesions not only afflict the sufferer, but also impose a large proportion of the burden of a debilitating disease [2]. The occurrence of neonatal hypothyroidism may not be the same in different parts of a country. Iodine deficiency and racial

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differences are among the most important factors for heterogeneity. Also, the use of different screening tests (T4 and TSH) can lead to differences in screening in different parts of a country. [3] The prevalence of maternal malnutrition in the world is on average one in three to four thousand births. In the United States, it is one in 4,500 live births, and in Europe, one in 3000 live births, and in some races like Hispanic, it reaches one in two thousand births [3] In Japan and North America, where iodine is consumed sufficiently, 7,000 and 4250 newborn infants develop hypothyroidism [4,5].

Studies in different parts of Iran have reported the prevalence of maternal hypothyroidism. For example, in Tehran, Shiraz, Isfahan, the prevalence of neonatal hypothyroidism was reported to be 1 in 914, 1 in 1465 and 1 in 342 births, respectively. Their similarities was prevalence higher than the global average [6]. Based on the results of numerous studies, many factors play a role in the incidence of the disease, including maternal age including maternal age above 40 years of age [7], delivery of cesarean section [7,8], affliction of hypothyroidism or goiter [9], diabetes [7,8], sexually transmitted diseases during pregnancy [7] and Asian race [7] increase the chance of congenital hypothyroidism. Babies weighing less than 2,000 and over 4,500 grams are at least 2 times more likely than those with low thyroid gland, and low thyroid gland in girls is more than boys [10]. The maternal delivery rate does not play an important role in the infant [7].

So far, several studies have been carried out to identify the congenital hypothyroidism risk factors that indicate the effects of multiple genetic and environmental factors on the onset of this disease [11-14], in which the genetic factors in the transient type and the environmental factors in its permanent type are more often referred to as the cause [15] that identifying these factors in controlling the disease and its complications is very helpful. Considering the high prevalence of congenital hypothyroidism in Mahshahr city, as well as its climatic conditions and the existence of different ethnicities due to the city's migratoryity, this study was conducted to evaluate the risk factors associated with congenital hypothyroidism and provide a preventive model.

Analysis method

This case-control study was conducted in Mahshahr city of Khuzestan province with a population of 260,000 people. The population of this study included all newborns born between 1389-1395 that selected by census method. In this method, all newborns born with congenital hypothyroidism were selected as cases and for each newborn infant in a healthy newborn in the same day and in the same area as the control group. The required data for the case group were extracted using the form number 3, which is related to the registration of children with hypothyroidism in the unit of diseases of the city's health center. Different stages of the diagnosis of hypothyroidism include taking 5 ml of blood from the heel of the baby's feet at 3-5 days by the Otolanst and transferring it to the 903 Watman filter paper. Samples were transferred to the reference laboratory located in the provincial capital after drying and were evaluated for TSH by ELISA method. According to the instructions of the Ministry of Health and Medical Education in Iran, the level of thyroid stimulating hormone TSH is greater than 10 mu / L and T4 level is lower than 6.5 mg per deciliter in the baby at birth as hypothyroidism. In addition, infants with a TSH level greater than or equal to 20 mu /1 are referred to a specialist. Infants with TSH levels below 5 mu / 1, and for infants aged 8 or more, TSH is considered to be less than 4 normal. According to the national guidelines, the normal range of T4 is considered to be mg/l 6/16-5/3, TS. 1/9-7/9,finally, infants with an abnormal screening result were considered as the case group and normal ones as the control group. Controls were randomly selected from infants who were normal for hypothyroidism. In this study, 104 newborns with congenital hypothyroidism were selected during each year and for each case a control from the same area of residence and the same day of birth were selected through random sampling.

Collecting data

The health records of the case and control group were collected from the health center in the area and a questionnaire containing information on the demographic status as well as the mother's condition during pregnancy including hypothyroidism, diabetes mellitus, asthma, preeclampsia, hypertension, drug use in pregnancy age and type of drug use, body mass index, number of pregnancy, mother's age, delivery season, delivery type, birth weight, infant's age, thyroid disease in the family were completed through a household health record. The neonate ethnicity was collected from the medical records unit at the birthplace of infants through a telephone call and the Apgar score of the infants through maternity medical records at the time of delivery.

Data analysis

Data were analyzed by SPSS software version 20. Data was analyzed using Chi-square, Fisher exact test and T-test (normal quantitative variables were investigated by Kolmogorov-Smirnov test). Then, the results of the regression model were compared with the model of diagnostic function (audit analysis). The significance level was considered to be $P \leq 0.05$ in all statistical tests.

Findings

A total of 208 neonates were enrolled in this study including 104 neonates of hypothyroidism and 104 healthy infants. Of 104 healthy infants, 52% (54 female) and 48% (50 male), of 104 unhealthy infants (56.7%) 59 male and 43.3% (45 female). There was no significant statistical relationship between the sexes of the newborn with hypothyroidism ($p = 0.21$). The history of thyroid disease in the mother was seen in 13 ones (12.5%) of the case group and 7 ones (6.7%) in the control group. The most frequent maternal delivery season in healthy and newborn babies was the winter season, which did not show a significant relationship between the incidence of neonatal hypothyroidism and maternal delivery season ($p= 0.96$). The

highest incidence in the case group was for mothers who did not have familial marriages In this regard, there was no significant statistical relationship between the disease and the marital status of the parents (p = 0.46). In relation to the ethnicity and the frequency of hypothyroidism, the most frequent cases of neonatal ethnicity in the case group were related to the Arab ethnicity and in the control group, the Arab ethnic group and the lowest The ethnicity of the infants was related to the Kurdish people (p = .30). In relation to the disease and the variable BMI, 55% of mothers in both groups of normal BMI and 7.2% of mothers in both groups had low body mass index (BMI), but no statistically significant relationship was found between congenital hypothyroidism and body mass index (28 / 0p =). In relation to other variables such as type of delivery, place of residence and mental disorders, there was no significant relationship with the disease (Table 1 and 2).

Table 1. Comparison of different qualitative variables in both case and control groups in single-variable analysis

variable	Case group	Control group	Chance ratio	CI 95%	P
	Number %	Number %			
Drug use during pregnancy	33 (31/7)	27 (25/9)	1/32	1/2-32/43	0/35
Mother's asthma	1 (0/96)	0	1	16-/20 0/62	1
Thyroid disease in the family	13 (12/5)	5 (4/8)	2/82	8- /24 0/97	0/049
Gestational age below 37 weeks	10 (9/6)	1 (0/96)	10/95	87-/23 1/37	0/005
Apgar Score	7 (6/7)	4 (3/8)	1/80	- 6/35 0/51	0/35
blood pressure	6 (5/7)	5 (4/8)	1/21	0/35 -4/1	0/096
Mother's pre-eclampsia	0	(0/96) 1	1	0/1-99/02	0/31
Diabetes	5 (4/8)	(3/8) 4	1/26	0/4-32/84	0/73

Table 2: Comparison of mean and standard deviation of different quantitative variables in case and control groups

variable	Case group		Control group		P
	mean	Standard variation	mean	Standard variation	
Baby weight (gr)	2995/385	613/063	3176/731	490/205	0/019
Number of pregnancies	2/26	1/24	2/26	1/22	1

Table 3. Multivariate logistic regression analysis of the association of some variables with neonatal hypothyroidism

Variable	chance ratio	CI 95%	P
Baby weight	1	0/99 – 1	0/32
Gestational age below 37 weeks	8/58	0/97 – 75/91	0/049
The history of thyroid disease in the family	3/03	1/03 – 8/88	0/043
blood pressure	1/2	0/341 – 4/57	0/8

As can be seen, in the multivariable regression analysis, the probability of being infected in neonates with a fetal age below 37 weeks is 8.58 times that of neonates over 37 weeks and the probability of being sick in newborns with thyroid disease in the family is 03.03 times more than the neonates without a history of thyroid disease in the family.

Table 4. Classification function coefficients in the single-variable healthy and patient group based on the diagnostic function model

variability	groups	
	healthy	patient
The history of thyroid disease in the family	11/17	12/154
Gestational age below 37 weeks	20/343	18/566
Baby weight	4/691	4/202

Based on this table, the coefficient of variation of thyroid in the family in the equation to identify the healthy group is 11/17 and for the patient group is 12/154. The coefficient of the fetal age variable below 37 weeks in the equation for identifying the healthy group is 20/343 and for the patient group is 18/566. The weight coefficient of the newborn weights in the equation for identifying the healthy group is 4/691 and for the patient group is 4/202.

Table 5. Comparison of the classification function results in the main groups based on single-variable mode with predicted results based on the model.

The studied variable	The predicted number of main group		The members of predicted group		Results of model comparison
			Healthy number (%)	Patient number (%)	
The history of thyroid disease in the family	healthy	104	99 (95/2)	5 (4/8)	53/8% The main groups are correctly categorized as % 8/53
	patient	104	91 (87/5)	13 (12/5)	
Gestational age below 37 weeks	healthy	104	103 (99)	1 (1)	% 3/54 of the main groups are correctly classified.
	patient	104	94 (90/4)	10 (9/6)	
Baby weight	healthy	104	94 (90/4)	10 (9/6)	% 4/54 are categorized correctly
	patient	104	84 (80/8)	20 (19/2)	

Based on this model, in the variable of thyroid disease in the family, the probability of correctly identifying healthy people is 95.2% and the correct identification of the patients is 12.5% and the cutoff in this model based on the thyroid disease variable in the family is 0.13, which is less than this number based on the equation in the patient group and more than this

number is placed in the healthy group. The ability to identify the model in the overall identification of healthy and patients is 53.8%.

In the fetal age of less than 37 weeks, the probability of correctly identifying healthy people is 99% and the correct identification of the patients is 9.6% and the cutoff in this model is based on the fetal variation below 37 weeks, which is less than this figure based on the equation in the patient group and more than this number is placed in the healthy group. The ability to identify the model in identifying patients and healthy people is 54.3%. In the neonate weight variable, the probability of correctly identifying healthy people is 90.4%, and the correct identification of the patient is 19.2% and the cutoff in this model based on the variables of the neonate's age is 0.15, which is less than this number based on the equation in the group more than this number in the healthy group. The ability to identify the model in the overall identification of the patient and the patient is 54.4%.

Table 6. Classification function coefficients in the patient and healthy group in multivariate mode based on the diagnostic function model

variables	groups	
	healthy	patient
The history of thyroid disease in the family	28/85	27/65
Gestational age below 37 weeks	42/33	40/83
Baby weight	1/6	1/3
Constant factor	-73/244	-67/195

The above table shows the diagnostic function coefficients for the healthy and patient group for the three variables, which shows that the gestational age below 37 weeks with a factor of 40.83 was higher than that of the thyroid disease in the family with a factor of 37.77 is more important factors in hypothyroidism.

Table 7: Comparison of the classification function results in the main groups based on multivariate mode with predicted results based on the model

The studied variable	The predicted number of main group	The members of predicted group		The result of the comparison model
		Healthy number (%)	Patient number (%)	
1- The history of thyroid disease in the family 2- Embolous age below 37 weeks 3- Baby weight	healthy 104 patient 104	89 (85/6) 69 (66/3)	15 (14/4) 35 (33/7)	6/6% of main group are categorized correctly

The probability of the correct identification of healthy people in this model is 85.6%, that is, of 100 healthy people 94 ones are identified correctly and the identification probability of the patient is 33.7%. This model has a low sensitivity and high feature. The cutting point in this model is based on the three-variable mode of 0.26 which is less than this number based on the equation in the patient group and more than this number in the healthy group. The ability to identify the model in the overall identification of patients and healthy is 59.6%.

Discussion

The aim of this study was to determine the risk factors associated with congenital hypothyroidism in neonates and to present a preventive model so that by using of risk factors and screening for hypothyroidism do the effective and timely diagnosis and treatment of hypothyroidism. In this study, there was no statistically significant relationship between sex and congenital hypothyroidism in 208 newborns born in Mahshahr province in Khuzestan province during the years 1395-1389. In a study by Hinton and colleagues in the (2010), the incidence of congenital thyroid function in recent years was equal in both of sexes. But in another study in Texas, as well as by Ismail Nasab and colleagues in Sanandaj (2012), the incidence of this disease was higher in boys than in girls [16, 17]. Although the results of the studies differ in this regard, it does not seem that the sex of the infant independently plays an important role in the development of the disease. In the present study, there was no statistically significant relationship between the number of mothers' pregnancies and type of delivery with disease in two groups. In a study done by Meda et al. (2005) in the United States, the association of the disease with the type of delivery was not meaningful but with parity of the mother [11]. The 2012 study in Kurdistan did not show a relationship between the disease and the number of maternal pregnancies [17]. In a study conducted by Keshavarziyan and colleagues in Shadegan (2016), there was no significant difference in the type of delivery with the disease [18]. In this study, no significant relationship was found between the fetal age and the sex of infants or the use of certain drugs during pregnancy.[18]. In another study in Hamadan, the results were similar in Shadegan [19]. In general, and according to the results of most studies, it can be concluded that the number of mother's pregnancy and type of delivery have no definite effect on the incidence of maternal hypothyroidism. In a single-variable analysis, the present study showed that there was a significant relationship between maternal hypothyroidism and embryonic age, birth weight and thyroid disease in the family, but there was no relationship between the use of the drug during pregnancy and congenital hypothyroidism. There was no significant relationship between gender, pregnancy and birth weight in a study conducted in the United States (2010) and another study in Yazd (2013). [16, 20]. In another study in the United States (2005), the type of delivery, birth weight, and embryonic developmental age of the newborn with a mother's hypothyroid had a significant but not significant correlation with maternal parity and infancy [11]. The discrepancy between the results of studies in this regard may be due to differences in the methods used in these studies or to the difference in congenital hypothyroidism and geographical areas. In a study in Isfahan, there was no significant difference between congenital hypothyroidism and seasonal variation, but the percentage of congenital hypothyroid was less than that in

the month of August and this percentage was lowest in December [21]. In a study conducted by Zainal Zadeh and his colleagues in East Azerbaijan (2014) and Dalili and colleagues in Gilan (2012), there was no significant difference between the two stages of labor and delivery in two groups [22, 23]. In our study, there was no meaningful relation between the delivery season and the illness in both case and control groups, which was consistent with other studies.

In a study conducted in Shadegan in 2014 in Khuzestan province, there was a significant relationship between congenital hypothyroidism and birth place in urban and rural areas [18]. Of course, in a study conducted by Osouli et.al in Tehran (2009), no specific geographical justification for the incidence of hypothyroidism was found in Iran, and other justifications for the risk of hypothyroidism among neonates were screened, including non-environmental and screening-dependent factors. [24]. In a study in Wales, England, which lasted 11 years, congenital hypothyroidism was lower in the southern regions than in the northern regions [25]. Another study by Harris and colleagues in New York (2007) found no significant correlation between the incidence of hypothyroidism in New York and other authors, and the author referred to the presence of some differences in high incidence rates in the Asian population in those areas. [26]. In our study, there was no significant relationship between congenital hypothyroidism and life in urban and rural areas. Rituals governing communities, soil conditions, and nutrition according to having iodine are different in different geographic regions, and in areas where iodine intake is lower by the mother during pregnancy, the risk of the disease in newborns rises and the lack of coordination between the results of studies may be due to differences in Methods used in these studies and different geographic areas.

There was a significant relationship between familial marriage and congenital hypothyroidism in the study of Shadegan in 2014 and Razavian et al in Hamadan province (2013) [18, 19]. In a study in Tehran, having a family history has been a protective factor for congenital hypothyroidism in neonates [24]. In the study of Shadegan and a study conducted by Qadiri and his colleagues in Kermanshah (2013), there was a significant relationship between congenital hypothyroidism and familial marriage [18, 27], but in a study conducted by Hashemipour and his colleagues in Isfahan (2013), no meaningful statistical relationship between Familial marriage and hypothyroidism were not observed [28]. In our study, there was no significant relationship between congenital hypothyroidism and familial marriage. There is a controversy between different studies on the relationship between familial marriage and congenital hypothyroidism, and further investigation is needed with larger sample size. In the present study based on the findings of single-variable and multivariate analysis, several factors affecting the neonatal hypothyroidism of neonates including embryonic age below 37 weeks, thyroid disease in the family and the weight of the baby were identified and the preventive model was designed and, in order to ensure efficiency the logistic regression of the results was compared with the diagnostic function prevention model that in this model, the coefficients for single or multiple variables were obtained by determining the cut-off point for identifying the healthy and patient group, and the sensitivity and specificity for the correct diagnosis of healthy and healthy individuals. The results of this model in single-variable and multivariate states showed that all variables in a single state have lower sensitivity and higher characteristics than multivariate state. The correct identification of them is more accurate than normal people and the less error classification is possible, but their probability of identifying them in the correct prediction of the patient is low and the classification of the error is probably high. In this study, embryonic age below 37 weeks compared to other variables in single-variable and multivariate mode, contributes more to the development of hypothyroidism, followed by the history of thyroid disease in the family and the weight of the baby with lower coefficients. This model, by determining the cut-off point to separate a healthy and patient group and having a high profile, can play an important role in the correct identification of healthy individuals from the patient.

Conclusion

The present study showed that fetal age below 37 weeks, birth weight and history of thyroid disease in the family compared with other variables increased the chance of congenital hypothyroidism. Therefore, it is necessary to avoid family history of thyroid disease in family members and to continue the thyroid test during pregnancy and to continue screening for children, by reducing the risk of pregnancy and reducing the birth of preterm infants, as well as the treatment of mothers with thyroid disease in pregnancy from the birth of a Hypothyroidism baby.

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