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Investigation of the Risk Factors for Congenital Hypothyroidism in Iran: A Population-Based Case-Control Study

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Abstract

Background

Congenital hypothyroidism (CH) is one of the most common causes of mental disability, which can be prevented in the case of early diagnosis and treatment. We aimed to study the some relevant risk factors for CH in neonates born in Khorasan Razavi Province, Iran.

Materials and Methods:

This was a population-based case-control study conducted on 97,380 neonates. The study population consisted of neonates born from April, 2016 to March, 2018 and undergone a screening program for CH. Overall, 530 neonates diagnosed with CH by a specialist were assigned to a case group and the remaining were considered as controls. Information was extracted from the Sina Electronic Health Record System (SinaEHR®, Iran). Bivariate and multivariate logistic regressions were carried out to determine the associations between independent variables and CH.

Results: Of the 97,380 neonates, the case and control groups included 530 (248 females) and 96,860 (47,061 males) newborns, respectively. In multivariate analysis, the use of neonate formula (adjusted odds ratio [AOR]=0.63; 95% confidence interval [CI]: 0.43-0.93, P=0.02), medication during pregnancy (AOR=1.29; 95% CI: 0.86-1.94, P=0.23), maternal hypertension (AOR=3.25; 95% CI: 1.15-9.19, P=0.03), maternal depression (AOR=2.19; 95% CI: 1.16-4.14, P=0.02), maternal diabetes (AOR=0.65; 95% CI: 0.51-0.83, P=0.001), consanguineous marriage (AOR=1.34; 95% CI:1.12-1.60, P=0.002), place of residence, and birth season after adjusting for confounding variable remained in the final model.

Conclusion: The study findings showed that birth season, place of residence, maternal hypertension and depression, and consanguineous marriage can be the main risk factors for CH. However, further studies are needed to analyze the findings of the present study to be more confident about the causality of these relationships.

Key Words: Congenital hypothyroidism, Iran, Neonatal screenings, Risk factors.

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1- INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common endocrine disorders and one of the causes of congenital mental disability, which can be prevented in the case of early diagnosis and treatment (1-3). The only effective way to diagnose CH is screening by laboratory methods, such as thyroid-stimulating hormone (TSH) or free thyroxine (T4) measurement in dried blood spots from the umbilical cord or heel of the neonates on a paper filter (4, 5). The main goal of the neonatal hypothyroidism screening program is to eradicate mental disabilities caused by this disorder in all countries it is implemented (6). Currently, it is being carried out in the U.S.A, Mexico, Western Europe, Japan, Australia, New Zealand, Eastern Europe, Asia, and Africa (7, 8). The neonatal hypothyroidism screening program has been running in Iran's health system since 2005 (9).

According to the American Academy of Pediatrics (AAP), normal T4 and high TSH, which do not cause neurological defects based on evidence, can be due to either thyroid dysfunction (permanent or transient), or delay in the development of hypothalamic-pituitary axis. Thyroid tests can be duplicated at the age of 2-4 weeks and the treatment starts if TSH remains high (10-13). Studies have shown that the incidence of CH is 1 per 3,000-4,000 births worldwide and 1 per 1,000 births in Iran (higher than global statistics) (9, 14, 15). Generally, the global incidence of this disease is estimated to be 1 per 3,000-4,000 live births and 1 per 3801 live births in Europe (16). According to studies conducted in Iran, the prevalence of hypothyroidism is equal to 1 per 443 live births in Fars, Iran, 1 per 338 live births in Isfahan, 3.4 per 1000 live births in Kerman, Iran, 3.3 per 1000 live births in Kashan, Isfahan Province, Iran, and 1.6 per 1000 live births in Mazandaran (17-21). A great number of studies conducted on the identification of CH risk factors suggested the effects of several genetic and environmental factors on the onset of the disease. These factors include gender, birthweight, race, age, route of delivery, birth order, prenatal drug abuse, parental educational level, and multiple gestation (22-25). Nevertheless, limited number of studies have investigated the CH risk factors among large populations based on the electronic health records data. Hence, the present study aimed to examine the most relevant risk factors for CH in neonates born in Khorasan Razavi Province, Iran, during 2016 to 2018.

2- MATERIALS AND METHODS

2-1. Study design and population

The present case-control study was conducted on the population covered by Mashhad University of Medical Sciences, Mashhad, Iran, from April 5, 2016 to March 8, 2018. In this study, all those who did not suffer from CH were regarded as controls; therefore, statistical power is guaranteed by the high number of controls per cases.

2-2. Methods

The statistical population consisted of all neonates visited the sampling center for a TSH screening test within 3 to 5 days after birth. Demographic and clinical information of these neonates was extracted from the Sina Electronic Health Record System (SinaEHR®), affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. Information about each persons' health records, including visits, prescriptions, test results, diagnosis, and health care reports, was recorded. This system includes medical records of about 5 million people covered by Mashhad University of Medical Sciences. The structure of electronic health records allows users to access all data at any time. All the information on patient visits was extracted from the database through

coding in Microsoft SQL Server. The extracted information included gender, birth season, place of delivery, type of neonate feeding, route of delivery, preterm birth, multiple gestation, prenatal drug abuse (any drugs), history of hospitalization, nationality, age, educational level, occupation, maternal hypertension, depression, diabetes, consanguineous marriage, and place of residence.

2-3. Measuring tools

In this study, a case refers to a neonate diagnosed with CH by a specialist after TSH testing based on protocols and rejection of TSH transient increase. To recognize these patients, the ICD-10 code of CH (E03.1) was used. Diagnosis of maternal hypertension, diabetes, and depression was based on ICD-10 codes, including 110, 111, and 115 for hypertension, E10 and E11 for diabetes, and F32, and F33 for depression.

2-4. Laboratory measurements

Blood sampling was performed in all the centers affiliated to Mashhad University 3-5 days post-birth. Accordingly, a few drops of blood were taken from the heel of the neonates using a lancet, and then poured onto a filter paper. After drying, the neonates' TSH samples were sent to the reference laboratory in the capital of province via express mail for further analysis and measurement using the enzyme-linked immunosorbent assay (ELISA). Based on the national protocol, the TSH < 5 and 4 mU/L for neonates aged 3-7 and ≥ 8 days were considered healthy, respectively, and other results were categorized as suspicious. A new blood sample was taken from the heel of the suspicious cases (TSH range: 5-9.9 mU/L), and the vein of other cases for further diagnostic examinations. The definitive diagnosis was made based on the specialists' views, and the diagnostic code E03.1 was embodied in the electronic medical records of the neonates.

2-5. Ethical consideration

The information included in the electronic health records was kept confidential, and any data disclosure or analysis was anonymous.

2-6. Inclusion and exclusion criteria

Only the newly diagnosed cases of CH screened in the health centers were included in the study. The cases and controls with missing data (i.e., more than three variables) were excluded from the analysis.

2-7. Data Analysis

The obtained data were inserted into SPSS software (version 22.0) for statistical analysis. First, the effects of each variable on the odds ratio (OR) of CH in infants were studied using the univariate binary logistic regression. Then, to determine the confounding effects of other variables, those with a p-value less than 0.2 were analyzed using the multivariate binary logistic regression at the 95% confidence interval.

3- RESULTS

A total of 97,380 neonates were examined in this study, 530 cases of whom diagnosed with CH by a specialist, were assigned to the case group, and others were regarded as the controls. According to **Table.1**, six variables, including birth season, type of neonate feeding, prenatal drug abuse, maternal hypertension, depression, diabetes, place of residence, and consanguineous marriage, were analyzed using the multivariate regression. After adjusting the effects of other variables, the results showed that the OR estimate of CH in the neonates born in the summer, autumn, and winter were lower than that in the newborns born in the spring by 32% (adjusted odds ratio [AOR]=0.68; 95% confidence interval

[CI]: 0.53-0.87, P=0.002), 36% (AOR=0.64; 95% CI: 0.50-0.81, P=0.000), and 50% (AOR=0.50; 95% CI: 0.38-0.64, P=0.000), respectively. In addition, the prevalence of this disease was lower in the neonates fed with neonate formula, compared to those fed with breast milk by 37% (AOR=0.63; 95% CI: 0.43-0.93, P=0.02). The OR of CH occurrence in the neonates whose parents had a consanguineous marriage was 1.34 times higher, compared to that in the newborns of parents with non-consanguineous marriage (AOR=1.34; 95% CI: 1.12-1.60, P=0.002). Furthermore, the OR of CH in neonates whose mothers were afflicted with hypertension and depression were 3.25 (AOR=3.25; 95% CI: 1.15-9.19, P=0.03), and 2.19 (AOR= 2.19; 95% CI: 1.16-4.14, P=0.02) times greater than that of the newborns whose mothers were not afflicted with these conditions. The probability of CH occurrence in the neonates living in rural and suburban areas was 1.79 (AOR=1.79; 95% CI: 1.44-2.22, P=0.000), and 1.44 times higher (AOR=1.44; 95% CI: 1.17-1.77, P=0.001), compared to that in the neonates living in urban areas. The significant relationship of CH with birth season, type of neonatal feeding, prenatal drug abuse, maternal hypertension and depression, place of residence, and consanguineous marriage indicates that these variables can be independent predictors of the disease.

Table-1: Analysis of univariate (unadjusted) and multivariate (adjusted) logistic regression by the characteristics of all neonates with CH (case) and without CH (control).

Variables		Univariate logistic regression			Multivariate logistic regression		
		P-value	95%CI	OR	P-value	95%CI	OR
Gender	Female			1			
	Male	0.409	0.91-1.28	1.08			
Season of birth	Spring			1			1
	Summer	0.000	0.49-0.79	0.62	0.002	0.53-0.87	0.68
	Autumn	0.000	0.47-0.76	0.60	0.000	0.50-0.81	0.64
	Winter	0.000	0.39-0.65	0.50	0.000	0.38-0.64	0.50
Place of birth	Other places			1			
	Hospital	0.23	0.27-1.37	0.61			
Feeding	Breast milk			1			1
	Infant formula	0.04	0.45-0.98	0.67	0.02	0.43-0.93	0.63
Delivery type	Caesarean			1			
	Vaginal	0.43	0.90-1.27	1.07			
Preterm birth	Mature			1			
	Preterm	0.25	0.17-1.61	0.52			
Twinship	No			1			
	Yes	0.28	0.12-1.86	0.46			
Medication during pregnancy	No			1			1
	Yes	0.000	1.38-2.86	1.99	0.23	0.86-1.94	1.29
History of hospitalization	No			1			
	Yes	0.60	0.41-1.66	0.83			
Mother's nationality	Iranian			1			
	Non-Iranian	0.45	0.58-1.27	0.86			
Mother's age	35≥			1			
	35<	0.21	0.71-1.08	0.87			
Mother's educational attainment	Literate			1			
	Illiterate	0.70	0.50-1.86	0.89			

Mother's job	Employed			1			
	Housewife	0.53	0.55-1.35	0.87			
Maternal hypertension	No			1			1
	Yes	0.001	1.91-14.04	5.18	0.03	1.15-9.19	3.25
Maternal depression	No			1			1
	Yes	0.001	1.52-5.07	2.78	0.02	1.16-4.14	2.19
Maternal diabetes	No			1			1
	Yes	0.012	0.59-0.94	0.74	0.001	0.51-0.83	0.65
Kinship between parents	No			1			1
	Yes	0.0001	1.20-1.71	1.43	0.002	1.12-1.60	1.34
Place of residence	Urbana areas			1			1
	Rural areas	0.000	1.53-2.33	1.89	0.000	1.44-2.22	1.79
	Suburban areas	0.000	1.22-1.83	1.49	0.001	1.17-1.77	1.44

OR: Odds ratio; 95%CI: 95% Confidence interval.

4- DISCUSSION

The aim of this study was to evaluate some of the possible risk factors for the incidence of neonatal hypothyroidism. After adjusting the effects of other potential confounding variables, the results of multivariate regression analysis indicated that birth season, place of residence, maternal hypertension and depression, and consanguineous marriage still remained significant in the final model. The current study had a very large sample size and population-based nature; moreover, it used the electronic medical record system for data extraction. Regarding this, it can be stated that this study is the most extensive one in its kind in Iran, investigating new variables. In the present study, all members of the population other than cases were considered as the controls in order to increase the statistical power and eliminate the selection bias. The CH is one of the most common and preventable causes of mental disability, which lacks any clinical symptoms (26, 27). The onset of treatment for CH varies from place to place. In a study conducted by Saiami et al. in Mazandaran province, Iran, the CH treatment was initiated at the age of 21 days. Meanwhile, in Greece, Italy, and Turkey, the therapeutic procedures for CH were started at the ages of 17, 28, and 23 days, respectively (28-30).

Studies in Shiraz, Isfahan, and Tehran (Iran), have shown that the prevalence of CH is 1 per 1,000 births. On the other hand, this prevalence has been reported as 1 per 4,500, 3,000, and 5,700 births in the U.S.A, Europe, and Japan, respectively (16, 18, 31, 32). The results revealed no significant difference between male and female neonates in terms of chance of affliction with CH. However, studies in Europe and the U.S.A have shown that the probability of hypothyroidism was higher in female neonates. On the contrary, in the studies performed by Ismailnasab et al. in Kurdistan, Iran, and Abedi et al. in Sanandaj, Iran, the incidence of hypothyroidism in male neonates was higher than that in female ones (12, 14). The findings obtained by Rezaian et al. in Hamadan, Iran, and Zeinalzadeh et al. in Markazi province, Iran, are consistent with the results of the present study (33, 34). According to our results, no significant relationship was observed between the disease and prenatal drug abuse, which is in line with the findings reported by Rezaiean et al. (34). In the current study, there was no significant relationship between the route of delivery (i.e., caesarean section or vaginal delivery), and development of CH. However, Shojaifar and Vahdat reported that the prevalence of CH was higher in neonates born through vaginal delivery (35). The results of this

study also indicated that the chance of developing the disease was higher in the neonates of the mothers with hypertension and depression than that in the newborns whose mothers were not afflicted with these conditions by 2.19% and 3.25%, respectively. In addition, the prevalence of CH was higher in the neonates whose parents had a consanguineous marriage. Studies conducted by Keshavarzian et al. in Khuzestan province and Rezaian et al. in Hamedan, also corroborated the effectiveness of consanguineous marriage in increasing the probability of CH. Nonetheless, Zeinalzadeh et al. reported no relationship between these two variables (33, 34, 36). Regarding the relationship between the place of residence and incidence of CH, the results showed that the prevalence of the disease was higher by 79% and 34% among the neonates living in rural and suburban areas, respectively, compared to that in the newborns living in urban areas.

This is inconsistent with the findings reported by Keshavarzian et al. demonstrating that the incidence of hypothyroidism in neonates born in urban areas was 3.4 times higher than that in the newborns born in rural areas (36). The results of this study showed that the prevalence rates of hypothyroidism in the neonates born in the summer, autumn, and winter were lower than that in the newborns born in the spring by 32%, 36%, and 50%, respectively. This result is inconsistent with the findings of a study conducted in Markazi province, Iran (33). The findings of the present study can be applied in the identification of vulnerable groups and the establishment of some programs for the prevention and control of CH. Since CH is a preventable disease, some measures, such as regular control of blood pressure, pregnant women's blood sugar, mothers' increasing awareness, and knowledge about hypertension, diabetes, depression, and side effects of prenatal drug abuse, can be greatly helpful in increasing the survival rate of neonates and reducing the rate of the disease.

4-1. Limitations of the study

One of the limitations of the present study was that even small differences were statistically significant due to the very large size of the samples; however, these differences would be clinically negligible. Another weakness of the present study was the simultaneous investigation of hypothyroidism and its risk factors, which makes it difficult to examine temporal relationships. Although the same training was provided for the participants, there would be some differences in data collection methods and interview procedures in different sampling centers.

5- CONCLUSION

The study findings showed that the season of birth, place of residence, maternal hypertension and depression, and consanguineous marriage can be affected CH. However, further studies are needed to examine the findings of the present study and other studies in order to be more confident about the causality of the relationships. On the other hand, many of the factors investigated in this study are preventable, and therefore can be taken into account by the health policymakers.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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