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Risk Factors of Congenital Hypothyroidism Using Propensity Score: A Matched Case-Control Study

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ABSTRACT

Background: The aim of this study was to investigate the relationship between congenital hypothyroidism and several variables using two different adjustment methods.

Methods: This matched case-control study was conducted in Hamadan Province, the west of Iran, in 2012 enrolling neonates born between 2005 and 2011 and covered by screening program for congenital hypothyroidism. The neonates with TSH titer more than 10 mU/l or T4 titer less than 6.4 µg/dl were considered as cases. Each case was individually matched for birth place and year with four neonates with normal TSH and T4 titers as controls. The data were analyzed using two different approaches including propensity score and multiple conditional logistic regression model.

Results: Of 1313 enrolled neonates, 277 (159 girls) were cases and 1036 (531 girls) were controls. The most important prognostic factors which had significant effect on congenital hypothyroidism included twin, birth season, maturity, jaundice at birth, birth weight, age at pregnancy, maternal anemia and goiter, gestational age, delivery type, father's education and smoking status, and consanguinity. The associations reported by logistic regression were stronger that of than propensity score analysis in most items, although the differences were not statistically significant.

Conclusions: We addressed the effect of numerous potential risk factors on congenital hypothyroiditis and the impact of these factors on the disease occurrence. However, future prospective studies are needed to test these findings and hypothesis and to investigate the true effect of these potential risk factors on congenital hypothyroiditis.

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Introduction

Congenital hypothyroidism, caused by thyroid hormone deficiency at birth, is a major preventable cause of mental retardation worldwide [1]. According to previous evidence, the incidence of this disorder is reported in Iran one per 1000 in Kerman Province [2], 1.7 per 1000 in Gilan Province [3], and 2.7 in Isfahan Province [4] while the global average of congenital hypothyroidism (CH) is estimated one per 3000 to 4000 live births [1]. After eradication iodine deficiency in Iran [5], the pilot project for screening CH started in 2003 by the Ministry of Health and Medical Education and then was performed throughout the country in October 2005 [6]. The main goal of this screening program was early detection and treatment of neonates with CH in order to prevent from severe complications of the disease such as mental retardation, cretinism, and neonatal mortality [7-9].

Several studies have been conducted to investigate CH and its associated risk factors. Based on the current evidence, several individual and environmental factors have effect on CH such as gender, birth weight, race, age, consanguinity, parental education, type of labor, birth order, twin and drug usage during pregnancy [10-13]. However, the issue of confounding is key in epidemiologic inference and practice. When there are several potential risk factors and the question of interest is to assess the net relationship between CH and each variable separately, it is necessary to investigate the association between one factor at a time and the outcome of interest while adjusting for all other variables.

There are several strategies to minimize the effect of confounding variables. The practice of matching is particularly common and useful in the context of case-control studies when trying to make cases and controls as similar as possible regarding the potential confounders. However, matching may be logistically difficult in certain situation, particularly when there are multiple variables [14]. Another alternative approach for controlling confounding variables is using regression techniques. Multiple regressions allow the examination of the effects of all exposure variables simultaneously adjusting for all the other variables in the model. However, the results may be unstable when the exposure variables are numerous and the sample size is limited.

Another alternative approach for minimizing the effect of confounding variables is regression models such as multiple logistic regression analysis. The third alternative adjustment approach is so called propensity score [15]. This method was suggested for the first time by Rosenbaum and Rubin in 1983 [16]. This method which has recently yielded increasing use in health related investigations [17] allows matching on several variables simultaneously using conditional probability.

The aim of this study was to investigate the net relationship between CH and several variables using and comparing two different adjustment approaches including propensity score versus multiple logistic regression model.

Methods

In 2005, a national screening program for early detection of CH was conducted by Iranian Ministry of Health and Medical Education (MOHME) throughout the country and has been in progress up to now. Most of the data used in this study was extracted from the database recorded the results of this screening program. This program is a part of the legal responsibility of MOHME which is necessary for evaluation of the common diseases, monitoring of the surveillance system and health policy, thus no written or verbal consent was taken from the participants for their information to be stored in the database or being used anonymously for research. Additional data was collected through interview with parents after explaining the objectives of the study for them. Since no intervention was carried out in this study, we just took parents' verbal informed consent to participate in this study and answer to our questions. The response rate of 87.5% documents the process. The local Human Subject Review Board of Hamadan University of Medical Sciences approved this consent procedure (No 4642).

This matched case-control study was conducted in Hamadan Province, the west of Iran, in 2012 enrolling all neonates born in this province between 2005 and 2011 covered by screening program for congenital hypothyroidism. The neonates who had incomplete medical records in the local health centers or had no accessible mailing address were excluded from the study. In the screening program, blood samples had already been taken from all neonates' heel in order to detect hypothyroidism in the early neonatal period. The neonatal TSH titer more than 10 mU/l or T4 titer less than 6.4 μg/dl was considered as CH [18]. The neonates with CH were considered as cases. For each case, four neonates with normal TSH and T4 titers were selected as controls with the same birth place and year as the related case. Accordingly, the cases were individually matched with the associated controls to the one to four for birth place and year.

However, because of large number of variables investigated in this study, we used propensity score to assess the net effect of each variable controlling the potential confounding effects of the other variables. Propensity score for each individual was defined as conditional probability of being in the relevant group (cases or controls) given the predictive variable being identified for that individual as follows [16]:

Propensity Score = $pr\,(Z_i = 1|X_i=x_i)$

In this formula, $Z_i = 1$ if the subject is a case and $Z_i = 0$ if the individual is a control. X_i represents a vector of predictor variables in subject i for which the cases and controls were matched. Then, conditional logistic regression model was used to estimate the propensity score.

We investigated the effect of 19 potential risk factors on congenital hypothyroidism. The available data were extracted from the neonates' medical records using a checklist of items including demographic characteristics of the neonates such as sex, birth date and weight, jaundice, twin, birth place, birth order, and demographic characteristics of the parents such as educational level, age at pregnancy, type of delivery, mothers' occupation, and maternal anemia. Additional information was collected through interview with parents during home visit including consanguinity, maternal history of hypothyroiditis or goiter, and using medications during pregnancy such as levothyroxine, liothyronine, metimasol or carbimasol.

In order to control and minimize the effect of potential confounding factors, data were analyzed using two different adjustment approach including simple and multiple conditional logistic regression model and propensity score. All statistical analyses were performed at 0.05 significance levels using statistical software Stata 11 (StataCorp, College Station, TX, USA).

Results

Out of 1313 neonates enrolled in this study, 277 (159 girls) were cases and 1036 (531 girls) were controls. For 72 cases, we found less than four matched controls. The response rate was 87.5%. The neonates' mean birth weight was 2998.7 (±19.7) gr. The mothers' mean age in last pregnancy was 30.3 (±0.18) years. The distribution of several characteristics of cases and controls and their associations with CH are shown and compared in Table 1.

According to the univarite conditional logistic regression analysis, odds ratio (OR) estimate of CH was 1.71 in twins compared to singletons (*P*=0.004).

Table 1: Analysis of simple (unadjusted) and multiple (adjusted) conditional logistic regression as well as propensity score approach by the characteristics of the cases and controls (Pseudo $R^2 = 0.4489$)

	Subjects		Unadjusted Conditional Logistic			Adjusted Conditional Logistic [a]			Matched Propensity Score		
Variable	**Cases**	**Controls**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Gender											
Boy	118	505	1.00	-	-	1.00	-	-	1.00	-	-
Girl	159	531	1.29	0.98, 1.69	0.065	1.15	0.80, 1.66	0.434	1.20	0.86, 1.68	0.283
Twin											
No	230	929	1.00	-	-	1.00	-	-	1.00	-	-
Yes	47	107	1.71	1.18, 2.47	**0.004**	1.31	0.78, 2.19	0.302	1.49	0.92, 2.40	0.106
Birth season											
Spring	83	364	1.00	-	-	1.00	-	-	1.00	-	-
Summer	61	218	1.25	0.86, 1.81	0.244	1.28	0.76, 2.15	0.352	1.33	0.83, 2.14	0.234
Fall	46	244	0.83	0.56, 1.23	0.344	0.86	0.51, 1.45	0.561	0.95	0.58, 1.55	0.828
Winter	87	210	1.83	1.29, 2.59	**0.001**	2.45	1.53, 3.94	**0.001**	2.26	1.44, 3.54	**0.001**
Birth order											
1st	56	214	1.00	-	-	1.00	-	-	1.00	-	-
2nd	58	248	0.90	0.59, 1.36	0.614	0.64	0.36, 1.15	0.138	0.77	0.46, 1.29	0.320
3rd	49	180	1.08	0.69, 1.70	0.731	0.70	0.37, 1.29	0.245	0.79	0.46, 1.37	0.403
4th	68	206	1.31	0.86, 2.01	0.205	1.03	0.57, 1.89	0.932	1.21	0.73, 2.03	0.458
5th or more	46	188	0.95	0.60, 1.51	0.828	0.90	0.46, 1.74	0.756	1.02	0.58, 1.80	0.937
Maturity											
Mature	213	929	1.00	-	-	1.00	-	-	1.00	-	-
Premature	64	107	2.65	1.86, 3.77	**0.001**	3.56	2.10, 6.04	**0.001**	2.81	1.81, 4.37	**0.001**
Jaundice at birth											
No	127	738	1.00	-	-	1.00	-	-	1.00	-	-
Yes	150	298	2.96	2.25, 3.91	**0.001**	3.47	2.38, 5.05	**0.001**	3.39	2.41, 4.78	**0.001**
Birth weight (gr)											
2500-3500	140	435	1.00	-	-	1.00	-	-	1.00	-	-
<2500	86	311	0.84	0.62, 1.15	0.276	0.96	0.63, 1.45	0.832	0.91	0.62, 1.34	0.640
>3500	51	290	0.51	0.35, 0.73	**0.001**	0.51	0.31, 0.82	**0.006**	0.55	0.35, 0.85	**0.007**
Maternal age (yr)											
18-35	228	758	1.00	-	-	1.00	-	-	1.00	-	-
36-43	49	278	0.60	0.43, 0.84	**0.003**	0.54	0.34, 0.84	**0.007**	0.61	0.40, 0.92	**0.019**
Mathers' educational level											
Academic	35	147	1.00	-	-	1.00	-	-	1.00	-	-
Non academic	242	889	1.13	0.76, 1.67	0.537	1.29	0.56, 2.98	0.549	1.14	0.70, 1.87	0.589
Maternal job											
Housewife	243	913	1.00	-	-	1.00	-	-	1.00	-	-
Working	34	123	1.04	0.70, 1.56	0.833	1.10	0.46, 2.64	0.828	0.89	0.54. 1.49	0.675
Maternal anemia											
No	211	900	1.00	-	-	1.00	-	-	1.00	-	-
Yes	66	136	2.07	1.48, 2.89	**0.001**	2.28	1.43, 3.65	**0.001**	2.11	1.37, 3.25	**0.001**
Maternal smoking											
No	274	1021	1.00	-	-	1.00	-	-	1.00	-	-
Yes	3	8	1.38	0.37, 5.22	0.634	1.21	0.22, 6.86	0.822	1.00	0.22, 4.50	0.997
Maternal goiter history											
No	219	940	1.00	-	-	1.00	-	-	1.00	-	-
Yes	58	96	2.74	1.90, 3.97	**0.001**	3.46	2.06, 5.83	**0.001**	3.05	1.91, 4.88	**0.001**
Father's educational level											
Academic	46	287	1.00	-	-	1.00	-	-	1.00	-	-
Non academic	231	749	1.91	1.36, 2.70	**0.001**	1.72	1.09, 2.70	**0.019**	1.69	1.11, 2.56	**0.014**
Father's smoking											
No	209	878	1.00	-	-	1.00	-	-	1.00	-	-
Yes	68	158	1.85	1.33, 2.58	**0.001**	1.71	1.08, 2.69	**0.022**	1.54	1.01, 2.34	**0.043**
Gestational age (week)											
37-40	118	578	1.00	-	-	1.00	-	-	1.00	-	-
<37	64	107	2.94	2.02, 4.28	**0.001**	ND	ND	ND	1.24	0.80, 2.00	0.317
>40	95	351	1.31	0.96, 1.77	0.086	1.15	0.78, 1.71	0.477	1.21	0.83, 1.77	0.324
Delivery type											
Vaginal discharge	65	567	1.00	-	-	1.00	-	-	1.00	-	-
Emergency CS	145	381	3.42	2.46, 4.76	**0.001**	3.15	2.09, 4.76	**0.001**	2.85	1.97, 4.14	**0.001**
Elective CS	67	88	6.97	4.54, 10.72	**0.001**	7.44	4.19, 13.20	**0.001**	6.28	3.82, 10.34	**0.001**
Consanguinity											
No relation	110	760	1.00	-	-	1.00	-	-	1.00	-	-
2nd degree relatives	57	179	2.33	1.61, 3.38	**0.001**	2.25	1.40, 3.60	**0.001**	1.91	1.25, 2.90	**0.003**
3rd degree relatives	110	97	7.99	5.58, 11.45	**0.001**	7.95	4.97, 12.70	**0.001**	6.30	4.17, 9.49	**0.001**
Drug usage during pregnancy											
No	239	890	1.00	-	-	1.00	-	-	1.00	-	-
Yes	38	146	0.95	0.62, 1.44	0.800	0.96	0.53, 1.76	0.917	1.08	0.66, 1.76	0.755

[a] Adjusted for all variables shown in the table; ND: No data

The neonates who were born in winter were significantly at higher risk of CH compared to those neonates born in spring (*P*=0.001), however, there was no association between other seasons and congenital hypothyroidism. The OR estimate CH was 2.65 in premature neonates compared to mature ones (*P*=0.001). The OR estimate of CH among neonates with jaundice at birth was 2.96 compared to those neonates without jaundice (*P*=0.001). There was no significant difference between the occurrence of CH among normal and low birth weight neonates. However, neonates with birth weight greater than 3500 gr had lower risk of CH compared to neonates with normal weight. The neonates who were born to mothers older than 35 years (*P*=0.003), or mother who had anemia (*P*=0.001) or goiter (*P*=0.001) during pregnancy or mothers with gestational age less than 37 or greater than 40 weeks were significantly at higher risk of congenital hypothyroidism. Furthermore, neonates who had smoking father had great risk of CH compared to those neonates whose fathers were nonsmokers (*P*=0.001). The chance of CH was higher among neonates with low educated fathers compared to those neonates with high educated fathers. Both emergency and elective cesarean sections increased significantly the risk of CH compared to vaginal delivery (*P*=0.001). In addition, the risk of CH was higher among neonates whose parents were married with second or third degree relatives (*P*=0.001). There was no statistically significant association between gender, birth order, mothers' educational level and occupation, maternal smoking, and using medications during pregnancy. Almost the same results were seen in multiple conditional logistic regression and propensity score analyses.

Discussion

We assessed the effect of 19 different potential risk factors on CH. When there are several risk factors affecting the outcome of interest, each variable may confound the effect of other variables. The term confounding refers to a situation in which a non-causal association between a given exposure and an outcome is observed as a result of the influence of the a third variable. A number of statistical techniques have been suggested to control confounding. The basic idea underlying adjustment is to use a statistical model in order to estimate what the association between the exposure and the outcome would be, given a constant value or level of the suspected confounding variables [19]. For this purpose, we used and compared two different statistical models for adjustment including multiple logistic regression and propensity score analyses. We assessed the effect of several potential risk factors of CH simultaneously using the two statistical methods to adjust for underlying confounding effect of other variables. The statistical power of logistic regression was higher for some associations and that of propensity score was higher for some others. However, the overall statistical power of the two methods was nearly the same and the results of the both methods were almost similar with no statistically significant difference.

Several studies have investigated different prognostic factors of congenital hypothyroidism. According to our findings, girls were at higher risk of CH than boys although the association was not statistically significant. Previous studies showed an association between gender and CH. Albert et al. [20] conducted a case control study on 1,053,457 live births in New Zealand in order to investigate the etiology of increasing incidence of CH. They reported that 86% of cases had ascintiscan, 67% of which had thyroid dysgenesis with a female to male ratio of 5.0:1.0. Hinton et al. [11] analyzed US data from 1991 to 2000 and showed that race, ethnicity, sex, and pregnancy outcomes have an effect on the incidence rate of CH, although there have been some inconsistencies and regional differences. The risk of CH was higher among twins. This finding was confirmed by previous similar studies [12,21]. Oliver et al. reported the incidence rate of CH 3.2 per 10,000 in singletons and 10.1 per 10,000 among twins [22].

Our findings showed a significant association between birth season and CH so that neonates born in winter were at higher risk of hypothyroidism compared to those born in spring. However, the results of previous literature were inconsistent regarding seasonal relationship. Rocchi et al. [23] reported no seasonal effect in Italy while Gu et al. [24] in Japan indicated that temperature and season had significant effect on congenital hypothyroidism. Ordookhani et al. [25] reported a significant correlation between winter and congenital hypothyroidism. One reason that may be attributed to this controversy may be the number of covariates assessed by different studies and the statistical methods of adjustment they used for analysis. Another reason is the environmental and genetic factors that may have affected the results.

According to our findings, gestational age less than 37 or more than 40 weeks increased the risk of congenital hypothyroidism. In other words, there was a U-shape correlation between gestational age and congenital hypothyroidism. Such a finding was reported by previous studies. Medda et al. [12] conducted a population-based case-control study and performed a multivariate conditional logistic regression and indicated that short (<37 weeks) and advanced (>40 weeks) gestational ages were significantly associated congenital hypothyroidism. In addition, Mao et al. [26] screened 387,926 infants and concluded that prevalence of CH is associated with gestational age.

Cigarette smoking by parents can increase the risk of congenital hypothyroidism. The association was statistically significant for smoking fathers but non-significant for smoking mothers due to sparse data. There were only 11 mothers who were smokers three of which had children with congenital hypothyroidism. Since the sample size for this subgroup was small, the association did not become statistically significant. Previous literatures reported that risk of CH was higher among neonates whose parents were smokers [12,22].

The risk of CH was higher among both low educated mothers and fathers. The results of previous literatures were inconsistent. Medda et al. [12] showed no relationship between parents' educational level and CH while Connelly et al. [27] reported an inverse relationship between mothers' educational level and congenital hypothyroidism.

Both emergency and elective cesarean sections increased the risk of congenital hypothyroidism. McElduff et al. [28] investigated to determine whether neonates delivered by cesarean section have higher risk of CH than neonates delivered vaginally. They assessed 2031 infants and concluded that TSH levels was greater among babies

Like any match case-control study, an important limitation of this study was finding control subjects with the same birth place and year as that of the cases. For 72 out of 277 cases, we found less than four matched controls. However, this study had a number strengths and implications. First, effect of several risk factors were investigated simultaneously using two different adjustment methods including multiple logistic regression and propensity score to control for confounding and to obtain net effect of each variable. These statistical approaches reduced the possibility of confounding and made the results more reliable. Furthermore, Pseudo R-squared was 0.4489. That means the proportion of the total variability of the outcome that is accounted for by the variables in the model. Accordingly, the model could predict the predisposing factors effecting CH very well. These results may be useful for preventive screening programs and can be used for high-risk populations.

Conclusion

We addressed the effect of numerous potential risk factors on congenital hypothyroiditis and the impact of these factors on the disease occurrence. However, future prospective studies are needed to test these findings and hypothesis and to investigate the true effect of these potential risk factors on congenital hypothyroiditis. Furthermore, most of these factors are preventable or at least modifiable and should be focus of special attention by the policymakers who plan preventive screening programs in order to detect and manage high-risk populations.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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