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ORIGINAL ARTICLE

Determining the incidence and risk factors of congenital hypothyroidism based on the specifications of infants in Shadegan city in the period of 2006-2014: a case-control study

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ABSTRACT

Introduction: Congenital Hypothyroidism (CHT) is a condition in which the thyroid stimulating hormone (TSH) is equal to or more than 10 MU/L and the thyroxine hormone (T4) is less than 6.5 M/L. CHT is one of the most important preventable causes of mental retardation in infants. The present study aimed to determine the incidence of CHT and the associated factors.

Method: At first, a descriptive research was done to examine the incidence of CHT in the period of 2006-2014 in Shadegan city, Khuzestan province. Then, a case-reference and a case-control study was done to investigate the relationship between CHT and demographic characteristics, environmental factors and medical factors. The cases in this study were neonates with CHT (transient and permanent). The results showed that the venous TSH score for these neonates was equal to or higher than 10 MU/L and their T4 level was lower than 6.5 MU/L. The subjects in the control group were infants that did not suffer from CHT whose venous TSH and T4 scores were lower than 10 MU/L and higher than 6.5 MU/L, respectively. The relationship between the aforementioned factors with the illness was determined using multiple logistic regression statistical model. The SPSS 18 software was used to analyze the findings of this research.

Findings: In this study, the incidences of neonatal CHT in Shadegan were 17, 21.5 and 12.59 per thousand newborn infants in 2012, 2013 and 2014, respectively.

Conclusion: The parents' record of consanguineous marriage increases the likelihood of developing CHT; therefore, couples that wish to marry have to be educated and made aware in marriage counseling centers, both in the field of consanguineous marriage and CHT.

Keywords: incidence, screening, transient, permanent, congenital hypothyroidism

INTRODUCTION

Congenital Hypothyroidism (CHT) is one of the most common preventable causes of mental retardation (1). In most cases, this disease is asymptomatic, which is due to the passage of the thyroid hormone through the placenta and its entry into the fetus. Congenital abnormalities are seen in 10% of CHT cases. Cardiovascular abnormalities or cardiovascular abnormalities are among the most common of such abnormalities; however, hearing disorders, nervous system disorders, cleft palate and urogenital disorders are not uncommon either (2). CHT does not usually have many symptoms and only in about 5% of cases, some symptoms are shown in the first days after birth. These symptoms are rare and nonspecific, and this disease is usually not "clinically diagnosed" in the early days of life (2).

World Health Organization (WHO) recommends a daily intake of at least 90 µg of iodine in children under 5, 12 µg in children between 6 and 12 years of age, 150 µg in teenagers over 12 years and 250 µg during pregnancy and lactation (3). The prevalence of CHT varies in different parts of the world and it is directly related to iodine deficiency. The incidence of CHT is 1 in 4500 live births in the United States, 1 in 3000 live births in Europe, and 1 in 5700 live births in Japan (4). Skordis (2006) conducted a study and showed that the incidence of CHT was 1 in 800 live births in Greece. They also concluded that the incidence was twice as high in girls as in boys and 35 times higher in patients with Down Syndrome, meaning that these patients were 35 times more likely to develop CHT (5). A study done by Hashemipoor et al. (2005) showed that the incidence of CHT was 1 per 1000 live births in Isfahan. In a cross-sectional study done by them in the Isfahan province in 2013, it was concluded that the prevalence of permanent CHT was 1 in 1133 live births and the most important cause of CHT was hereditary thyroid hormone deficiency. Ordookhani (2010) did a study in Tehran province, in which the incidence of CHT was reportedly higher in the fall and the winter (6). Waller's study showed that the likelihood of incidence of CHT was two times higher in infants weighing less than 2000 g than other infants. Additionally, the incidence likelihood in the infants weighing more than 4500 g was twice higher than other infants. In other words, the effect of the weight of the infants on this disease was u-shaped, meaning that infants weighing less than 2000 g at birth and infants with macrosomia weighing more than 4500 g were twice more likely to have CHT than infants weighting between 2000 and 4500 g. Therefore, the relationship between birth weight and CHT was u-shaped (7). In the study conducted by Kopp in 2000, it was shown that CHT was usually sporadic and that genetic factors play a very small role in its incidence (8). The research conducted by Murphy (2004) showed that premature infants were at a higher risk for this disease (9). In the study done by Herbstman (2008), it was concluded that the number of mother's births did not play role in the incidence of this disease in newborns. Furthermore, in this study, the cesarean delivery was recognized as a risk factor (10). The study conducted by WHO (2007) showed that iodine played a key role in thyroid hormone synthesis. By performing neonatal screening in any population, infants with CHT can be detected and diagnosed very quickly. Early diagnosis of CHT could prevent or reduce the pain felt by the family and

it would also help the doctors obtain important information in the field of epidemiology and physiopathology of this disease in that population. According to previous studies, neonatal screening for CHT is a preventive medical program with a positive cost-benefit ratio. The majority of benefit-cost ratios have been estimated based on the financial burden imposed on the society to care for mentally retarded children. Even though various aspects of family life have yet to be taken into consideration, studies have shown that screening prevents wasting a large portion of the budget. The estimated cost of the screening program is similar in various parts of the world, which is approximately between 0.7 and 1.6 dollars per screening for each infant. In the United States, diagnosis of a neonatal hypothyroidism and its timely treatment saves 2228 dollars. Currently, the practical method of the implementation of the screening program is the use of dried blood samples on filter paper; which is easier, more practical and cheaper than serum samples. Additionally, the half-life of the analyte, especially at room temperature on filter paper, is longer than that of the serum sample. In general, two TSH and T4 tests are used on filter paper to perform the screening. Both tests are equally sensitive in detecting neonatal hypothyroidism; however, some believe that the initial TSH test is more sensitive. In addition, TSH concentrations remain constant on filter paper for a longer period of time than T4. For these reasons, TSH test was selected as the initial screening test in this research. Currently, the following methods are used to perform screening in the world:

In the CHT screening program in Iran, a sample is taken from the heel of the infant on the 3rd to 5th day after birth on a special filter paper approved by the Ministry of Health. The prepared samples are dried at room temperature (they should not be dried with heat), then placed in a special envelope and sent to the provincial screening laboratory by post (selected in accordance with the provincial operational plan). The samples should not be placed in a damp place or be contaminated with other materials. Distorted, contaminated, or folded samples are unusable and thus, another sample should be taken from the babies. The samples have to be prepared with maximum precision in accordance with the sampling instructions to reduce the error probability as much as possible. According to the findings of the previous studies conducted in Iran, the following features and sensitivities were chosen for the available kits in the CHT screening program: The Cut-Off points of equal to or more than 10, 4, and 3 MU/L for the samples prepared on a filter paper in the first week of birth, from the eighth day of birth up to 5 months after birth, in infants older than 5 months who are breastfeeding, respectively. According to the decision of the National Committee, values between 5 and 9.9 MU/L are reported to a pediatrician or endocrinologist (focal-point of the program) and the treatment is done based on the doctor's judgment (either the screening test is done again and/or the patient is supervised). It is obvious that another decision might be made and executed in association with the initial tests between 5 and 9.9 MU/L after the first year of the implementation of the program. Due to the high incidence of CHT in Shadegan, a study was conducted on the incidence and risk factors of CHT over the period of 2006-2014. The overall goal of this project was to determine the incidence and factors associated with CHT in Shadegan city from 2006 to 2014.

METHODOLOGY AND MATERIALS

At first, a descriptive research was conducted, in which the incidence of CHT was examined in three periods of 2006-2014, 2006-2012, and 2012-2014 in Shadegan. In addition, in this section of the study, the incidence of the disease was studied based on age, gender and season of the year. Then, the relationship between CHT and demographic characteristics, environmental factors, and medical factors was examined using a case-reference and a case-control study.

The patients and the newborns diagnosed with neonatal CHT in the aforementioned period of time were selected to study the entire population. The population of cases (patients with CH) were 207 definite cases, 4 of whom were cases from before 2012 and 203 of whom infants diagnosed with CHT from 2012 to 2014. In addition, three controls were selected for each case to increase the precision of the study. The simple randomized sampling technique and the random number table were used to select the controls. These controls were selected out of the infants that did not suffer from CHT based on their birth year (i.e. the cases and the controls were similar in their year of birth). Overall, there were 657 controls, 100 of whom were selected from Khoramshahr and another 100 were selected from Abadan.

The cases were patients who were actually diagnosed with CHT, using TSH and T4 (or free T4) serum concentration tests. During infancy (1-4 weeks), T4 and TSH of the patients diagnosed with CHT were lower than 6.5 MU/L and equal to or higher than 10 MU/L, respectively. Furthermore, if the concentration of TSH was higher than 20 in the selected infants, a venous sample was first taken and then the treatment immediately started in accordance with the instruction. After receiving the results of the serum test, if the infant suffered from CHT, the drug was continued and adjusted if necessary, and if the infant was healthy, levothyroxine tablet intake was stopped.

The controls were newborn infants without CHT whose initial TSH test was lower than 5 MU/L or infants whose venous TSH and T4 test results were lower than 10 MU/L and equal to or higher than 6.5 MU/L, respectively.

All infants born in the period from 2006 to 2014 were at risk for CHT during that time period. This population was equal to 2651, 3237, 3522, 3524, 3723, 3884, 3900, 3991, and 4050 infants in 2009, 2010, 2011, 2012, 2013, and 2014, respectively.

To calculate the cumulative incidence, the new cases of infants diagnosed with CHT were selected as the numerator and the neonatal population born in the beginning of the same year were selected as the denominator and then the fraction was multiplied by 1000. The difference between cumulative incidence and incidence density is that cumulative incidence is unitless, while incidence density has a time unit. The dominator for cumulative incidence is the population in the beginning of the period, whereas it is person-time or average population in incidence density. Cumulative incidence is a proportion,

while incidence density is a rate. Range is between 0 and 1 in cumulative incidence, while it is between 0 and ∞ in incidence density. For these reasons, cumulative incidence was selected for this study.

Methods of avoiding bias in research

1- Using the random number table to select the controls to prevent selection bias.
2- Using information collection form to collect the necessary information about the cases and the controls to prevent recall bias.
3- Using the Masking of Interviewers technique to prevent interviewer bias.
4- Using the Protocol method to prevent interviewer bias.
5- Using information collection form to collect the necessary information about the cases and the controls to prevent respondent bias.
6- All infants are screened and volunteers are not screened to prevent selection bias.
7- Selecting all the population to prevent selection bias.

Examination of environmental factors: to study the environmental factors, three water samples were taken from the International Wetland of Shadegan (Fig. 1) in Sarakhieh village by environmental health engineers and the samples were examined and evaluated in terms of nitrite, nitrate, iodine, and chlorine using a spectrophotometer (hack dr2000 model made in USA). Sampling was done to confirm the hypothesis regarding the relationship between CHT and toxins such as nitrite, nitrate and chlorine.

Data analysis method: the frequency distribution and central and dispersion indices were used to describe the data and the multivariate logistic regression statistical model was used to determine the relationship between the aforementioned variables and the disease. The SPSS 18 software was used to analyze the research data.

Findings

Description of data from 2006 to 2014

Given that the period from 2006 to 2014 was reviewed in this research, after reviewing the data provided in the patient files in the area under study, it was seen that there were no cases from 2006 to 2008; thus, the results associated with the years 2009 and later were examined. It should be noted that there was only one case in 2009, 0 in 2010 and 3 cases in 2011. As a result, the data of the year 2012 and later were analyzed. Out of the 3524, 3723, 3884, 3900, 3991, and 4050 infants screened in 2009, 2010, 2011, 2012, 2013, and 2014, cumulative incidences of CHT were observed in 0.28, 0, 0,77, 17, 21.5, and 12.59, respectively, per thousand live births. Table 1 shows the descriptive results of this research from 2006 to 2014 (%%%).

Table 1 – description of CHT per thousand live births

Cases and controls (2006-2014)	Case	Control
Gender	Number (percentage)	Percentage
Male	116(56%)	317(47%)
Female	91(44%)	353(53%)
Total	207	670

	2009	2010	2011	2012	2013	2014
Population at risk	3524	3723	3884	3900	3991	4050
Number of patients	1	0	3	66	86	51
Cumulative incidence	0.28	0	0.77	17	21.5	12.59

Gender of the infant	2009	2010	2011	2012	2013	2014
Cumulative incidence of the disease in male patients	0.5	0	1	22.6	22.5	14.3
Number of male patients	1	0	2	43	45	29
Cumulative incidence of the disease in female patients	0	0	0.5	12.1	22.5	10.8
Number of female patients	0	0	1	23	41	22

Season	2009	2010	2011	2012	2013	2014
Spring	0	0	0	12.3	27.08	11.85
Summer	1.13	0	1.02	20.5	39.13	17.91
Fall	0	0	2.05	19.5	10.03	13.93
Winter	0	0	0	13.38	10.03	5.97

Type of hypothyroidism	2009	2010	2011	2012	2013	2014
Permanent	0.28	0	0.25	0.75	0	0
Transient	0	0	0.51	13.5	21.5	12.4

Table 2 – cumulative incidence, population at risk, number of patients, and gender of patients with CH

	2006	2007	2008	2009	2010	2011
Population at risk	2561	3237	3522	3524	3723	3884
Number of patients	0	0	0	1	0	3
Cumulative incidence of the disease	0	0	0	0.28	0	0.77
Number of male patients	0	0	0	1	0	2
Number of female patients	0	0	0	0	0	1

Description of data from 2006 to 2011: The total number of patients suffering from CHT from 2006 to 2014 was 4 people, with one male patient in 2009 and three patients in 2011 (two male patients and one female patient). Table 2 shows the cumulative incidence, number of patients, population at risk and gender of patients diagnosed with CHT in Shadegan city from 2006 to 2011.

Description of data from 2012 to 2014: There were 203 patients with CHT from 2012 to 2014, with 80, 92, and 61 cases in 2012, 2013, and 2014, respectively. Out of all patients, 113 were male and the other 90 were female patients. Table 3 displays the results of the descriptive study from 2012 to 2014.

The results of the multivariate logistic regression analysis showed that there was no relationship between the season of the year and CHT, compared to other variables. This means that distribution of the disease was the same in different seasons. In addition, there was no relationship between the gender of the patients and CHT, compared to other variables. There was a relationship between parents' consanguineous marriage and CHT, compared to other variables. According to this finding, the cases were 2.4 times higher than the controls in terms of parents' consanguineous marriage (Tables 4 and 5).

To analyze the environmental factors, a water sample was taken from the International Wetland of Shadegan by environmental health engineers on 06.10.2015 at 8:00 AM at 21 °C and 67% humidity. Based on the results of the chemical water tests, the average nitrate, nitrite, and iodine in the three water samples were 0.8, 0.1, and 0.24 MG/L, all of which were below the standard. Furthermore, the chlorine in water was reported to be 0 on the same date.

The result of examining the relationship between the risk factors and transient CHT in Shadegan city from 2012 to 2014: The results of the multiple logistic regression analysis showed that there was no relationship between the season of the year and CHT, meaning that the distribution of the disease was the same between various seasons. There was no relationship between CHT and the infant's weight of below 2000 g and above 4000 g, meaning that the distribution of the disease was the same between different weight groups. There was no relationship between gender and CHT. There was a relationship between the parents' consanguineous marriage and CHT, meaning that the cases' record of consanguineous marriage was 2.3 times more than that of the controls (Table 6).

Table 3 – Description of data from 2012 to 2014

	2012	2013	2014
Population at risk	3900	3991	4050
Number of patients	66	86	51
Cumulative incidence	17	21.5	12.59

	Case	Control
Gender	Number(%)	Number(%)
Male	113(55%)	314(47%)
Female	90(44%)	343(53%)
Total	203	657

Type of CH		2012	2013	2014
Transient		13.5	21.5	12.4
Permanent		0.75	0	0

	2012	2013	2014
Transient	54(81%)	86(100%)	51(100%)
Permanent	12(19%)	0	0
Total	66	86	51

Table 4 – Frequency and percentage of variables in the cases and controls in this study from 2012 to 2014

Variable		Case(%)	Control(%)	P-Value
Gender	Male	113.203(55)	314.657(48)	0.54
	Female	90.203(45)	343.657(43)	
Prematurity of the newborn infant	Yes	6.201(3)	18.657(3)	0.81
	No	195.201(97)	639.657(97)	
Season	Spring	51.199(26)	142.657(22)	
	Summer	76.199(39)	230.657(35)	
	Fall	43.199(22)	151.657(23)	
	Winter	23.199(12)	134.657(20)	0.22
Type of birth	Natural	135.203(66)	447.657(68)	0.73
	Cesarean	68.203(34)	210.657(32)	
Record of consanguineous marriage	Yes	116.203(57)	297.657(45)	0.004
	No	87.203(43)	360.657(55)	

Table 5 – The results of examining the relationship between the risk factors and CHT using the logistic regression analysis from 2012 to 2014

Variable	Category	OR (95%CI)	P-Value
Gender	Female	1	
	Male	1.39(2.22-0.97)	0.07
Season	Winter	1	
	Spring	1.2(2-7.22)	0.444
	Summer	1.37(0.2-8.32)	0.243
	Fall	1.10(1-61.96)	0.744
History of consanguineous marriage	No	1	
	Yes	2.41(1.3-65.53)	<0.001
Type of birth	Cesarean	1	
	Natural	1.11(1-75.65)	0.584

Table 6 – The results of examining the relationship between the risk factors and transient CHT in Shadegan from 2012 to 2014

Variable	Category	OR (95% CI)	P-Value
Gender	Female	1	
	Male	1.36(1-94.97)	0.09
Season	Winter	1	
	Spring	1.38(0.2-76.49)	0.28
	Summer	1.39(0.2-8.41)	0.23
	Fall	1.15(0.2-63.1)	0.64
Type of birth	Cesarean	1	
	Natural	1.08(1-72.61)	0.70
Record of consanguineous marriage	No	1	
	Yes	2.35(1.3-59.47)	<0.001

DISCUSSION

In the present study, the incidence and the factors associated with CHT in Shadegan were determined in the period of 2006-2014. The incidences of neonatal CHT in Shadegan were 17, 21.5, and 12.59 per thousand newborn infants in 2012, 2013, and 2014, respectively. This finding indicates that incidence of disease in Shadegan was significantly higher than the rate of incidence with one case of neonatal CHT per 1000 live births (11). The study conducted by Ordookhani et al. (2014) in Iran showed that the incidence of CHT in Iran was 1 per 1000. Additionally, based on their findings, there was a significant relationship between the high incidence of CHT and the high prevalence of consanguineous marriage in Iran (28). Hashemipoor et al. (2005) showed that that the incidence of CHT was 1 per 1000 live births in Isfahan. In a cross-sectional study (2013), it was concluded that the prevalence of permanent CHT was 1 in 1133 live births in Isfahan. The findings also showed that the most important cause of CHT was hereditary thyroid hormone deficiency (12, 13, 14, 15).

The results of this study showed that there was a relationship between CHT and history of consanguineous marriage. This means that infants with parents who have a record of consanguineous marriage are 2.4 times more likely to be diagnosed with CHT than those without a record of consanguineous marriage. The study of Ordookhani et al. (2010) showed that the incidence of CHT in newborns in Tehran was 2-3 times more than its rate in the world. It was also shown that this rate had a significant relationship with the high prevalence of consanguineous marriage. In addition, the chance of diagnosis with CHT was 2.7 in people with a record of consanguineous marriage, which confirms the hypothesis stating that consanguineous marriages significantly influence the incidence of CHT (11). Thus, consanguineous marriage could be considered as one of the factors contributing to the higher incidence of CHT in Iran (11). A case study conducted by Rezayiyan (2013) displayed that the incidence of CHT had a significant relationship with parents' record of consanguineous marriage in Hamedan province. In this research, it was found that many infants with CHT had a history of consanguineous marriages in their families (2.2 times more than infants without the disease), which confirms the hypothesis regarding the role of consanguineous marriages in CHT. In the study conducted by Kopp, it was argued that CHT was usually sporadic and genetic factors played a very small role in its incidence (19). In the research done by Hashemipour et al., no significant relationship was seen between CHT and consanguineous marriage in Isfahan (14, 12, 13).

In this study, no significant difference was found in the relationships between the examined variables of gender – season – infant weight – type of labor and CHT. In Greece, the incidence of CHT was 0 per 800 live births and incidence of CHT was 2 times more likely in girls than boys and it was 35 times more in down syndrome patients (5). Waller showed that the likelihood of incidence of CHT was two times higher in infants weighing less than 2000 g and those weighing more than 4500 g than other infants. In other words, the effect of the infants' weight on this disease was u-shaped. Waller also concluded that this disease was seen more in girls than in boys (7). According to Ordookhani's study, the incidence of CHT was reportedly higher in fall and winter (6). In the research conducted by Hashemipour et al., it was shown that the highest incidence was observed in August (15). The study of Herbstman showed that in cases where the mother was older than 40 years old, the age of the mother was a risk factor as far as CHT was concerned. Furthermore, cesarean birth was also

identified as a risk factor (10). However, WHO argued that cesarean was not a risk factor for the CHT disease (3).

CONCLUSION

The history of parents' consanguineous marriage enhances the chance of developing CH; therefore, couples who wish to marry have to be educated and made aware in marriage counseling centers both in the field of consanguineous marriage and CHT. Additionally, urbanization increases the chance of CHT development. Since the mother's daily intake of iodine is the most important risk factor for CHT, it is recommended to pregnant mothers to pay special attention to their iodine intake in their diet during their pregnancy by eating fish and other seafood. The physicians, midwives, and health workers should also be especially educated and pay particular attention to this field. Also, it is recommended to assess the urinary iodine levels of pregnant mothers and to record their test results in their files so that the incidence of CHT can be prevented in time.

REFERENCES

1. Skordis N, Toumba M, Savva S, Erakleous E, Topouzi M, Vogazianos M. al.High prevalence of CHT in the Greek Cypriot population results of the neonatal screening program 1990-2000. Pediatr Endocrinol. 2005;18(5):453-61.
2. Ordookhani A, Mirmiran P, Najafi R, Hedayati M, Azizi F. CHT in Iran. Indian J Pediatr 2003; 70: 625-8.
3. McElduff A, McElduff P, Wiley V, Wilcken B. Neonatal thyrotropin as measured in a CHT screening program. influence of the mode of delivery J ClinEndocrinol Metab. 2005; 90(12): 6361-3.
4. Hashemipoor M, Amini M, Iranpour R, Sadri G, Javaheri N, Hagighi S. Pervalence of CHT in Isfahan, Iran results of a survey on 20000 neonates. Horm Res 2004; 62(2): 79-83.
5. Karamizadeh Z, Amirhakimi G. Incidence of CHT in Fars Province, Iran. Irn J Med Sci 1992; 17: 78-80.
6. Kopp P. Pendred's syndrome and genetic defects in thyroid hormone synthesis. RevEndocr MetabDisord 2000; 1(1-2): 109-21.
7. Ordookhani A, Pearce E, Mirmiran P, Azizi F, Braverman L. Transient CHT in an iodine-replete area is not related to parental consanguinity, mode of delivery, goitrogens , Iodine exposure, or thyrotropin receptor autoantibodies. J Endocrinol Invest. 2008; 31(1): 29-34.
8. J. Wolff Perchlorate and the Thyroid Gland. Pharmacological Reviews 1998; 50(1): 89-105.
9. Braverman L, EN EP, He X, Pino S, Seeley M, Beck B. Effects of SixMonths of Daily Low-Dose Perchlorate Exposure on Thyroid Function in Healthy Volunteers. The Journal of Clinical Endocrinology & Metabolism. 2006; 91(7): 2721-4.
10. Nagayama J, Kohno H, Kunisue T, Kataoka K, Shimomura H, Tanabe S. Concentrations of organochlorine pollutants in mothers who gave birth to neonates with CHT. Chemosphere. 2007; 68(5): 972-6.
11. Law W, Bradley D, Lazarus J, John R, Gregory J. CHT in Wales (1982-1993): demographic features, clinical presentation and effects on early neurodevelopment. Cline Endocrinal (Oxf) 1998; 48: 201-7.
12. Hashemipour M, Amini M, Kelishadi R, Hovsepian S, Haghighi S, Hosseini M. Seasonal variation in the incidence of CHT in Isfahan, Iran. Saudi Med J. 2007; 28(10): 1582-6.
13. Medda E, Olivieri A, Stazi M, Grandolfo M, Fazzini C, Baserga M. Risk factors for CH: results of a population case-control study (1997-2003). European Journal of Endocrinology. 2005; 153: 765-73.
14. Gittoes N, Franklyn J. Thyroid drug-induced disorders. Drug Safety 1995; 13: 46-55.
15. Waller D, Anderson J, Lorey F, Cunningham G. Risk factors for CH: an investigation of infant's birth weight, ethnicity and gender in California, 1990-1998. Teratology. 2000; 62(1): 36-41.