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A systematic review on the risk factors of congenital hypothyroidism

Running title: Risk factors of congenital hypothyroidism…

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Abstract

Context: Congenital hypothyroidism (CH) is the most common endocrine disorder and causes of preventable mental retardation in children. **Objectives:** We aimed to systematically review the reported congenital hypothyroidism (CH) related risk factors. **Data Sources:** In this systematic review, all types of human studies studying the risk factors related to the occurrence or high rate of CH were included.An electronic search was conducted in international national electronic databases. The following keywords were used ;("Congenital Hypothyroidism" [Mesh] AND "risk factor" [Mesh]).**Study Selection:** In this review, 373 papers (PubMed: 199; Scopus: 36; ISI: 53, SID: 55, Ovid: 11; Science Direct: 19) were identified through electronic database search.98 articles assessed for eligibility, from which 60 qualified articles were selected for final evaluation. Most of the studies have cross sectional, case control and prospective design, respectively. **Data Extraction:** The current review was conducted and reported in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) statement. **Results:** Reported risk factors for transient CH were as follows; iodine deficiency and excess, prematurity, advances maternal age, male gender, retinopathy of prematurity, twin pregnancy, maternal autoimmune thyroid disease, intrauterine growth retardation and cesarean delivery. Reported risk factors for permanent CH with dysgenesis of thyroid gland were as follows; female gender, familial history of CH, birth in geographical areas with high rate of the disease, advanced maternal age, ethnicity (Caucasians) but not seasonality. Reported risk factors for permanent CH with dyshormonogenesis were familial history of CH and origin of both parents from the high risk geographical region. **Conclusions:** Using the data we could plan more etiologic studies to investigate the pathogenesis of the disorder, design interventional studies for the known modifiable risk factors to reduce the rate of CH in our region. In addition for risk factors with limited evidences more studies should be performed.

Key words: Congenital hypothyroidism, permanent, transient, risk factor

1. Context

Congenital hypothyroidism (CH) is the most common endocrine disorder and causes of preventable mental retardation in children which is defined as at birth thyroid hormone deficiency (1,2). It is classified as primary and secondary. Primary causes include defects in thyroid gland development (thyroid dysgenesis) or deficiencies in thyroid hormone synthesis (thyroid dyshormonogenesis)(1,2).

CH screening program is considered the most practical and effective method of CH diagnosis as the disorder has not any specific sign and symptoms at birth and during neonatal period. It is a routine practice in developed countries and many developing countries. Findings of CH screening from different regions and countries indicated great variability in the incidence or etiology of CH. In accordance to CH screening, etiological factors and different risk factors of the disorder have been identified and reported in previous studies (3,4).

Findings of the studies demonstrated the importance of etiological studies for better understanding of the pathogenesis of CH as well as its related risk factors to conduct further preventative strategies. It is clear that the investigation of modifiable risk factors for CH is important because of the potential to prevent CH specially in regions with high rate of CH.

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 (5-8).It is believed that many other risk factors might influence on the occurrence of CH (5-12).

Confirming the cause and effect relationship between these risk factors and CH and identifying them might be helpful even in decreasing the incidence of CH. More practically, it can help to have a higher index of suspicion for CH in neonates with the identified risk factors.

2. Objectives

Though there are different studies in this field but the results are not comprehensive enough and it is suggested that systematically reviewing of CH related risk factors would provide us more appropriate information for designing our future etiological and preventative researches. So that we aimed to systematically review the reported CH related risk factors.

3. Data Sources

In this study we systematically reviewed all studies which investigated CH risk factors. The protocol of this study was approved by the regional ethics committee of Isfahan University of Medical Sciences.

An electronic search was conducted in international electronic databases including PubMed, Cochrane, Scopus, ISI web of Science, Ovid, Science direct and IranMedex, Irandoc, and Scientific Information Database (SID), were used for Persian document searches. The following keywords were used ;(“Congenital Hypothyroidism” [Mesh] AND “risk factor” [Mesh]) in Title/ abstract.

The latest search was conducted on 29th of September 2017.

4. Study Selection

In this review, all types of human studies studying the risk factors related to the occurrence or high rate of CH were included without any time limitation. Included articles published in the English and Persian language. The search was performed without any time limitation until September 2017.

Inappropriate or repeated papers were excluded.

The titles of all searched articles was reviewed and studied and repeated items were excluded.

The full texts of selected articles were carefully studied by two researchers and irrelevant papers were excluded. A secondary search was conducted from the references of selected papers.

5. Data Extraction

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist was used for reporting systematic reviews.

The quality of the documents was evaluated independently by the two research experts regarding the objective of each study, methods, sample size, sampling method, data collection tool, variable evaluation status, and evaluated target group. Disagreements were resolved by consensus and mutual discussion and consulting with an expert in the field of CH (MH).

Foreachfinallyincludedarticlethefollowinginformationwasextracted;authors,placeofthestudyand/orethnicity,yearofpublication,samplesize,studydesign and reported risk factors.

In this review, 373 papers (PubMed: 199; Scopus: 36; ISI: 53, SID: 55, Ovid: 11; ScienceDirect: 19 ;) were identified through electronic database search.98 articles assessed for eligibility, from which 60 qualified articles were selected for final evaluation (Figure1).

Details of all selected studies were presented in Table1 (5, 9, 8, 12-68).

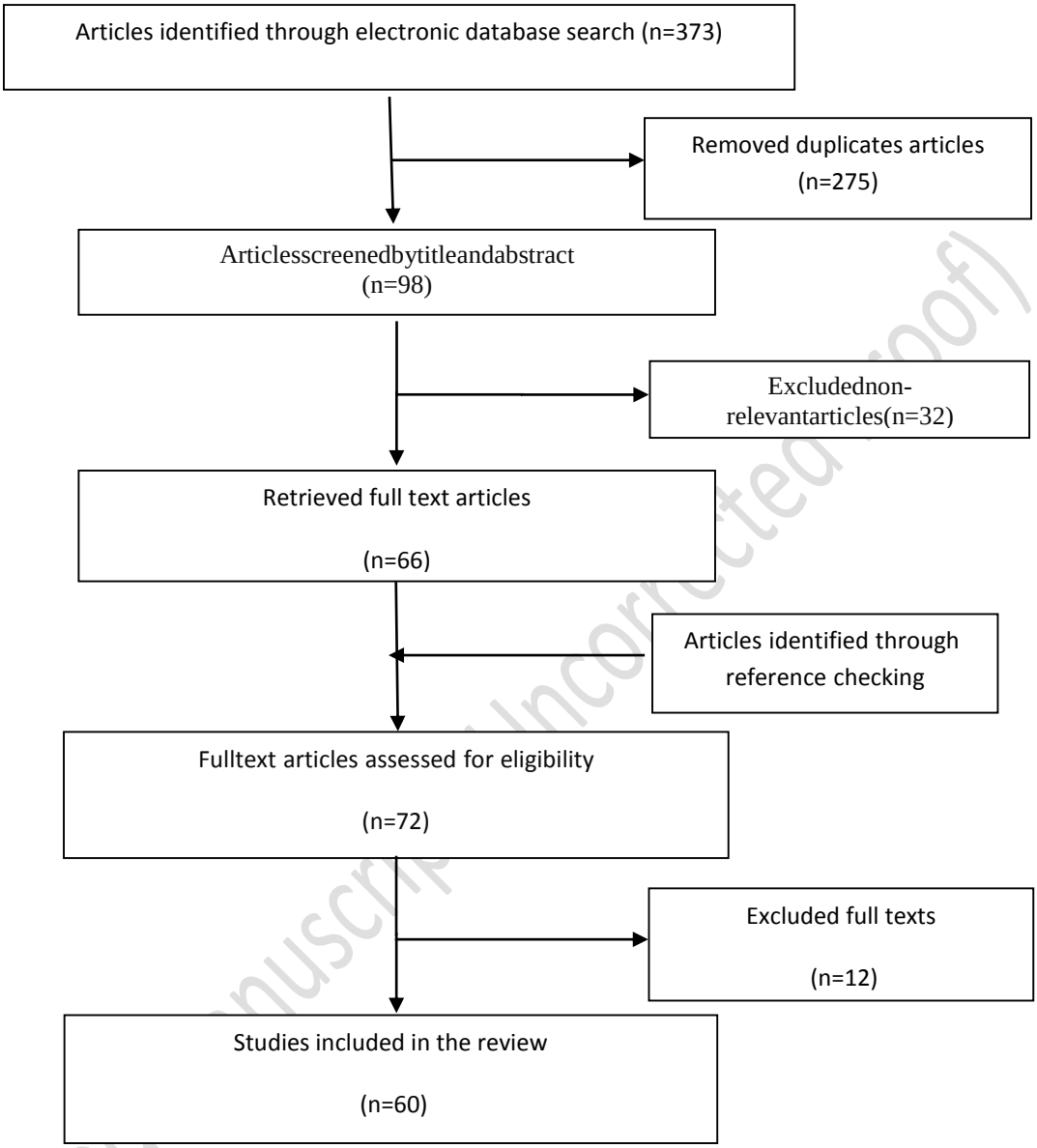

Figure1. Flowchart of study selection

Table1. Details of the papers

No	Name of first author, year ,place	Sample s size	Type of study	Type of CH	Reported risk factors
1	Thalhammer et al. 1981 Austria(13)	Resuts of CH screening since 1976	Cross sectional	Permanent CH	Seasonality
2	Meberg A et al. 1986 Norway(14)	46 smoker and 49 nonsmoker mothers	Case control	Serum TSH	Mother smoking
3	Rosenthal et al. 1988 England (15)	289697 screened eonates(November 1981 - February 1987)	Cross sectional	Primary CH	Parental consanguinity
3	Virtanen et al. 1989 Finland(16)	307,000 screened neonates	Cross-sectional	Permanent CH	Female gender, CH in the family, high risk geographic region, seasonality for dysgenesia History of CH in the family and high risk geographic region for dyshormonogenesis
4	Kaiserman et al. 1991 Israel(16)	303 primary CH patients	Cross sectional	Primary CH	-
5	Lorev et al. 1992 USA, California(17)	Over 5 million infants	Prospective	Primary CH	Female gender for all ethnic groups except blacks
6	Sorcini et al. 1994 Italy(18)	239 cases of CH	Prospective	Primary CH	Iodine deficiency
7	Dussault et al. 1999 Quebec, Canada(19)	259 mothers of CH newborns	Cross sectional	Transient CH	Maternal autoimmune thyroid disease(antimicrosomal antibodies)
8	Hall et al. 1999 England(20)	1128 632 neonates screened over 16 years	Cross sectional	Primary CH	Season, Parental consanguinity
9	Waller et al. 2000 California,The USA(12)	1806 cases of CH	Cross sectional	Primary CH	Low birth weight,macrosomia,ethnicity ,gender
10	Rocchi et al. 2001 Italy(21)	92 CH patients	Retrospective	Primary CH	-
11	Henry et al. 2002 Saudi Arabia(22)	44 CH patients from 121404 screened neonates	Cross sectional	Primary CH	-

12	Ordookhani et al. 2002 Tehran,Iran(23)	22 CH patients from 20107 screened neonates	Cross sectional	Primary CH	Parental consanguinity
13	Buyukgebiz A. 2003 Turkey(24)	-	Review paper	Transient CH	Prematurity
14	Ouhoummane et al. 2004 Canada(25)	32,978 screened newborns (1993-1999)	Retrospective	Primary CH	Chlorine dioxide (ClO_2) in disinfected water for low birth weight infants
15	Ordookhani et al. 2004 Tehran, Iran(26)	41 CH patients(6 of them transient CH)	Cross sectional	Transient CH	Exposure with iodinated disinfectants during perinatal period
16	Lian et al. 2005 China(27)	35 CH patients	Retrospective	Primary CH	Prematurity, modest or heavy hypertension during pregnancy,high serum anti-thyroid peroxidase antibodies levels
17	McElduff et al. 2005 Australia(28)	2031screened neonates	Cohort study	Primary CH	Cesarean delivery
18	Medda et al. 2005 Italy(29)	173 cases and 690 controls were enrolled in 4 years	Case control study	Permanent and transient CH	Twin birth, birth defects, female gender and gestational age >40 weeks , family history of thyroid diseases among parents,maternal diabetes for permanent CH intrauterine growth retardation, prematurity for transient CH
19	Deladoëy et al. 2007 Québec, Canada(5)	424 CH patients	Cross sectional	Permanent CH with dysgenesia	-
20	Ordookhani et al. 2007 Tehran,Iran(30)	48106 screened neonates	Cross sectional	Serum TSH	Cesarean delivery,
21	Hashemipour et al. 2007 Isfahan,Iran(31)	358 CH patients from 113282 screened neonates	Cross sectional	Primary CH	Month of birth, suspected environmental factors
22	Gu et al. 2007 Japan(32)	1586 CH patients	Cross sectional	Primary CH	Gender, season
23	Hashemipour et al. 2007 Isfahan,Iran(33)	274 CH patients	retrospective	Primary CH	1st cousin parental consanguinity
24	Olivieri et al. 2007 Italy(34)	3600 CH patients	Retrospective	Both transient and permanent CH	Twin birth, environmental factors

25	Mao et al. 2007 China(35)	289 CH patients	Cross sectional	Primary CH	Post term birth, low birth weight infants and macrosomia
26	Rowland et al. 2008 The USA (36)	-	Clinical inquiries	Primary CH	Prematurity, infants wellbeing(cerebralpathology, low Apgar scores, respiratory distress syndrome, persistent ductus arteriosus requiring treatment, necrotizing enterocolitis),maternal thyroid disease, iodine deficiency/excess
27	Eftekhari et al. 2008 Kerman,Iran(37)	23 CH patients from 3000 screened neonates	Cross sectional	Primary CH	gender, maternal age, families socioeconomic condition, parents education, mothers iodinated salt consumption, parents occupation, thyroid hormone use by mothers
28	Sepandi et al. 2009 Shiraz,Iran(38)	126 CH patients and 401 controls	Case control study	Primary CH	Parental consanguinity, birth defects, birth defects in first-degree relatives, female gender, twin births, prematurity
29	Cranston et al. 2010 California,The USA(39)	698 CH patients	Cross sectional	Primary CH	Prematurity, maternal age, civilian maternal status
30	Hashemipour et al. 2010 Isfahan, Iran(40)	68 CH and 178 healthy children and their mothers	cross-sectional study	Primary CH	Milk iodine concentration and iodine excess
31	Hinton et al. 2010 The USA(8)	142 CH patients from 47,075 screened neonates	Cross sectional	Primary CH	Race, ethnicity, sex, and pregnancy outcomes
32	Aminzadeh et al. 2010 Ahvaz, Iran(41)	142 CH patients from 47,075 screened neonates	A prospective two-year study	Permanent CH	Season
33	Hashemipour et al. 2010 Isfahan,Iran(42)	194 CH and 350 normal and their first-degree relatives	Case-control study	Primary CH	Hypothyroidism
34	Safar Alizade et al. 2010 Khoy,Iran(43)	16 CH patients	Prospective	Primary CH	Parental consanguinity, maternal diet during pregnancy(chicken)
35	Stoppa-Vaucher et al. 2011 Montréal, Canada(44)	190 patients with TD (147 ectopies, 40 athyreoses, and 3hypoplasias) and the 44 patients with DH	A case control study	Permanent CH with thyroid dysgenesis(TD)	Ethnicity

36	Hashemipour et al. 2012 Isfahan,Iran(45)	65 patients with CH and their mothers as case and 148 healthy neonates and their mothers as control groups	A case–control study	Primary CH	Maternal thyroid autoimmunity [Thyrotropin receptor antibodies (TRAb)]
37	Zeinalzadeh et al. 2012 East Azerbaijan, Iran(46)	94 CH patients from 62,459 screened neonates	A cross sectional	Primary CH	Maternal age
38	Ooki S. 2013 Japan(47)	18 CH patients	Retrospective study	Primary CH	Multiple births
39	Abdelmoktader et al. 2013 Egypt(48)	320 cases and 320 controls were enrolled in 8 years.	a population-based case-control study	Primary CH	Twin birth, birth defects, female gender, gestational age > 40 weeks, and gestational diabetes
40	Rezaeian et al. 2013 Hamadan ,Iran(49)	1313 enrolled neonates, 277 (159 girls) were cases and 1036 (531 girls) were controls	Case control	Primary CH	Twin birth, 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
41	Ng et al. 2011 Liverpool, UK(50)	6498 neonnates during CH screening	Retrospective	Primary CH	Low birth weight
42	Dalili et al. 2012 Guilan, Iran(51)	221 CH patients from 119701 screened neonates	Retrospective	Primary CH	Low birth weight, postdate delivery, macrosomia, vaginal delivery
43	Kirmızibekmez et al. 2012 Turkey(52)	234 CH patients	Retrospective	Permanent CH with dysgenesia	Maternal age
44	Rabbiosi et al. 2013 Italy(53)	84 CH patients and eutopic thyroid gland	Prospective	Permanent and transient CH	Prematurity, first-degree familial history of goiter/nodules for permanent CH Mild iodine deficiency for transient CH
45	Esmailnasab et al. 2013 Kordestan,Iran(54)	105 CH patients and 105 controls	Case control study	Primary CH	Familial thyroid disease
46	Rezaeian et al. 2014 Hamadan,Iran(55)	277 cases(CH patients) and 1036 controls	Case control	Primary CH	Interaction of gender (girl) and birth season (summer)
47	Dorreh et al. 2014	414 CH patients from 127 112 screened neonates	Cross sectional	Primary CH	Family history of thyroid diseases

	Arak,Iran(56)				
48	Uenaka et al. 2014 Japan(57)	35 pregnancies complicated by Graves' disease. 9 cases with neonatal thyroid dysfunction and 22 with normal thyroid function	Prospective	Primary CH	Maternal FT4 level
49	Fan et al. 2015 China(58)	1210 CH patients	Prospective	Transient CH	Iodine deficiency
50	Satoh et al. 2015 Japan(59)	212infants born to mothers who become pregnant after undergoing HSG involving the use of ethiodized oil	Prospective	Primary CH	Using ethiodized oil contrast medium during HSG
51	Mehrnejat et al. 2015 Isfahan, Iran(60)	667 CH patients from 275,485 screened neonates	A descriptive-analytic study	Primary CH	Nitrate concentration in drinking-water
52	Zhou et al. 2015 China(61)	125 neonates with CH (case group) and 375 neonates without CH (control group)	A case control study	Primary CH	Mother's age, gestational diabetes, gestational thyroid disease , birth weight , gestational age, foetus number, fetal distress, birth defects
53	Trumpff et al. 2015 Brussels, Belgium(62)	313 Belgian mothers and their 4- to 5-year-old children	A retrospective cohort study	Primary CH	Season, maternal smoking, lower weight gain during pregnancy, gestational age
54	Dayal et al. 2015 India(63)	80 CH patients	Retrospective	Permanent CH(dysgenesia)	Maternal age
55	Keshavarzian et al. 2016 Shadegan, Iran(64)	203 CH patients and 657 controls	Case control	Primary CH	Parental consanguinity, urbanization
56	Aguiar et al. 2016 Massachusetts, The USA(65)	76	Retrospective	Transient vs. permanent CH	Maternal age, Cesarean delivery, retinopathy of prematurity for transient CH
57	Blasig et al. 2016 Berlin, Germany(66)	84 CH patients	Cross-sectional	Primary CH	Serum Cu
58	Yang et al. 2016 China(67)	CH patients diagnosed during 25 years of CH screening	Cross sectional	Primary CH	Female sex, preterm birth, older gestational age, low birth weight, and preterm birth
59	Anastasovska et al. 2017 Macedonia(68)	46 CH patients	A 14-year retrospective cohort analysis	Primary CH	Ethnicity
60	Khanjani et al. 2017 Kerman, Iran(69)	773 CH patients from 288,437 screened neonates	Cross sectional	Primary CH	Season

6. Results

Most of the studies have cross sectional, case control and prospective design, respectively. Most of the studies evaluated the possible risk factors for primary CH. Reported risk factors for transient CH were as follows; iodine deficiency and excess, prematurity, advances maternal age, male gender, retinopathy of prematurity, twin pregnancy, maternal autoimmune thyroid disease, intrauterine growth retardation and cesarean delivery(19,24,26,34,52,57,64). Reported risk factors for permanent CH with dysgenesis of thyroid gland were as follows; female gender, familial history of CH, birth in geographical areas with high rate of the disease, advanced maternal age, ethnicity (Caucasians) but not seasonality(5,15,43,51,57,62).

Reported risk factors for permanent CH with dyshormonogenesis were familial history of CH and origin of both parents from the high risk geographical region (15). In five papers the risk factors effects on TSH level during screening wereevaluated (14, 25, 28, 30, 35).

7. Discussion

In this systematic review we studied all reported studies in the field of CH risk factors. Most of the review studies were cross sectional and evaluated the risk factors of primary CH. There were few studies investigating the risk factors of permanent vs. transient or different etiologies of CH. Though some of the reported risk factors for permanent and transient CH and different etiologies of permanent CH were similar but some of them were specific for the mentioned groups. By considering the reported group differences we could design more studies for better understanding of different subgroups of CH.

As mentioned previously, though there were studies regarding CH related risk factors (29,35,37,45,48,50,57,60,64) but there was not any comprehensive review in this field. In addition for some important risk factors such as seasonality or gender differences the results of different studies were not constant. We classified the risk factors in the following categories; known risk factors with enough and appropriate evidences, known risk factors with controversial results and risk factors with limited evidences which need more evaluations.

The role of some risk factors such as ethnicity, thyroid disorders in families, other birth defects, preterm and post term delivery, low and high birth weight, parental consanguinity and twin or multiple pregnancies for CH have been clearly determined in many studies(12,13,20,23-25,33,34,46,49,53,55,56,63,66,67). Though there were also few studies which did not report such an association but almost all of them support the role of above mentioned risk factors for CH. However the additive effect of the risk factors for occurrence of CH should be investigated in future researches.

Iodine deficiency and/or excess(18,26,35), gender (32,17), seasonality (5,13,20,21,22,31,68) maternal age (12,38,45,62,64), type of delivery(28,64) and maternal anti thyroid drug use(30,27) were the risk factors with controversial reports. Though their role as CH related risk factors for CH have been demonstrated in previous researches but the findings are not conclusive.

Iodine deficiency is one of the most important risk factors for CH, but by elimination of iodine deficiency in different countries, it seems that iodine excess is considered as risk factor for

CH(18,26,35). Iodine excess could be a result of different factors such as using iodinated salt and different pharmacological agents using for therapeutic or diagnostic procedures in specific disorders. Satoh et al. in Japan have evaluated the rate of thyroid dysfunction in neonates born to mothers who have undergone hysterosalpingography(HSG) involving an oil-soluble iodinated contrast medium. According to their findingsin the thyroid dysfunction group the median dosage of ethiodized oil was significantly higher than in the normal thyroid function group. They recommended that when infertile women undergo HSG, the administrated dosage of oil-soluble iodinated contrast mediumshould be reduce to minimize the risk of thyroid dysfunction in fetus or neonates(58).

Previous studies showed an association between gender and CH. Many reports have indicated that CH is frequently found in girls (12,15,17,29,32,37,45,47,54,57). According to previous evidences, females to males ratio was approximately 1.0 among hereditary cases of CH(32), moreover, this ratio was about 2.0 for the CH cases with both athyreosis and ectopia groups (17). Castanet et al. (69) reported that the female preponderance over males for isolated CH was similar to those with ectopic thyroid gland or athyreosis. Accordingly, the preponderance of female gender for CH is mainly related to thyroid dysgenesis. These results were also reported in another study (15).

According to our findings, girls were at higher risk of CH than boys. But there are also studies which did not show such an association (50).

Recently, Rezaeian et al. in Hamedan, Iran have studied the potential interactions that are able to change the effect of gender on congenital hypothyroidism(54).

They indicated that odds ratio estimates of CH for investigated factors (except for birth season) did not differ substantially between girls and boys. Similarly, Ng et al. found that there was no significant difference between girls and boys regarding gestation and birth weight in all etiological subgroups such as athyreosis and ectopia groups (49).

Rezaeian and colleagues have finally indicated that birth season might act as an interaction to increase the risk of CH in girls (54). However, it is unclear why girls have a higher incidence rate of CH than boys, while there is no difference in proportion of other risk factors between them.

So that, the reasons of gender differences deserve further investigations.

The results of reviewed literature regarding seasonal relationship were inconsistent. Gu et al. in Japan indicated that temperature and season had significant effect on CH. They reported that from January to December, males and females had one and two peaks,respectively (32). In the British Midland, higher incidences of CH were reported in fall between October and December (20).

Some studies did not report any seasonal pattern for CH. Rosenthal et al. observed no seasonal difference in the incidence of CH in the North West of England, in Asian families compared with non-Asians (70). No evidence of seasonal variations was reported during the CH screening program in Saudi Arabia and Italy(22,21)also. Kaiserman et al. in Israel conducted a 10-year temporal analysis of primary CH, the average monthly incidence showed a small peak in August, but, monthly incidences of CH had not significant periodicity (71).

There were different studies from Iran in this field. Ordookhani et al. reported a significant correlation between winter and CH.Hashemipour et al. (16) reported higher and lower incidence

rate of CH in summer and in the last month of autumn, respectively. They findings were not similar to others. They suggested that other factors such as exposure to different chemical compounds, seasonal environmental factors, and differences in climate might play role in the etiology of CH.

In previous studies in Iran, Aminzadeh et al. investigated the association between seasonal changes in temperature and the prevalence of congenital hypothyroidism (CH) in Southwest Iran, and they reported that the prevalence of CH has a significant negative correlation with temperature. The odds of being affected were increased by 4% for each fall of 1°C(40). Findings of other studies from Iran showed higher incidence of CH in autumn and winter.

The impact of environmental factors such as climatic conditions and seasonal changes in the incidence of CH is still unclear. In a recent study in Iran,Khanjani et al. for the first time have evaluate the effects of several climatic factors such as temperature, humidity, and rainfall on the incidence of CH.They did not find any significant association between CH and climate factors, in Kerman Province, whereas they reported highest rate of CH inOctober (Autumn) and lowest in June (Summer)(68).

It seems that the reported discrepancy may be due to differences in climate, living conditions, and various levels of iodine in different geographical areas. It is also suggested that different environmental and genetic factors could interact with seasonality and consequently could affect on the incidence of CH in each region.

Some studies reported advanced maternal age as a risk factor for CH(12,38,45).But some of them have reported such an association only for thyroid dysgenesis(64).According to the documents maternal age more than 35 years could be a risk factor for CH(48).

Type of delivery was another conflicting risk factor. McElduff et al. in their investigation among 2031 infants have indicated that TSH levels were greater among babies delivered by cesarean section (28).Rezaeian and colleagues also have reported higher incidence rate of CH in both emergency and elective cesarean sections (48).Whereas Ordookhani et al have indicated that cord blood TSH and rates of hyperthyrotropinemia are lower in cesarean section than in vaginal deliveries. They showed that povidone-iodine disinfection at delivery has an effect neither on TSH concentrations nor on the rate of hyperthyrotropinemia in the iodine-replete area of Iran (30). Similarly, Dalili et al. have reported that Rate of normal vaginal delivery (NVD) was significantly higher in neonates with CH compared to normal population (50). It seems that different condition related to the type of delivery including the iodine condition of the population, method of delivery and using different disinfectant have impact on the association of type of delivery and CH occurrence.

Some studies reported that maternal anti thyroid drug use and its pattern could affect on thyroid function of neonates (56, 27). Lian et al. in China have reported that the risk of abnormal thyroid function of infants whose hyperthyroid mothers did not take anti thyroid drugs until the third trimester of pregnancy may be increased (27). In one study using thyroid hormones by mother was not considered as a risk factor for CH.

Some of the reported risk factors including environmental pollutants(25,59),dietary component of mothers during prenatal period(42,65),neonatal jaundice(48), maternal anemia(48), intrauterine

growth retardation(29), lower weight gain during pregnancy(61), urbanization(63), parental occupation and education(36,48), gestational diabetes (29,47,60)and smoking(14,48,61)have limited evidences. It seems that more studies for investigation the association of the mentioned risk factors with CH is necessary. From the above mentioned risk factors some have great priority including environmental pollutants, smoking, gestational diabetes, and maternal anemia due to their importance in preventative medicine.

So far, few studies in the world have investigated the effect of environmental factors on CH incidence. Ouhoummane et al. in Canada have compared thyroid function of newborns from 11 municipalities where drinking water was disinfected by chlorine dioxide (ClO2) with that of newborns from 15 municipalities using chlorine disinfection. There was no significant increase in the TSH level and rate of CH when all newborns exposed to ClO2 were considered. However, for newborns with low birth weight, mean TSH level was significantly higher among those exposed to ClO2 than for those in the reference group. They concluded that Chlorine dioxide (ClO2) is considered a risk factor for CH in preterm and low birth weight neonates (26).In another study in Iran,Mehrnejat et al. did not find a significant relationship between nitrate concentration in drinking-water and incidence of CH through linear regression analysis (59).

In two studies, dietary component of mothers have been reported as risk factor for CH including Cu deficiency and some dietary components (65,42). It seems that evaluation the association of prenatal dietary components would be helpful for identification of CH related modifiable risk factors.

The limitation of current review was the heterogenicity of papers, so that we could not have meta analysis in this field.

The strength of this review was its novelty. There was not any systematic review regarding the risk factors of CH.

8. Conclusions

The findings of current review provide us baseline information about reported CH related risk factors from different countries. Using the data we could plan more etiologic studies to investigate the pathogenesis of the disorder, design interventional studies for the known modifiable risk factors to reduce the rate of CH in our region. In addition for risk factors with limited evidences more studies should be performed.

Moreover, discrepancies between different studies regarding CH related risk factors also may be due to the fact that the consequences of interaction of different risk factors in different populations with different genetic background, different environmental factors and neonatal, maternal, and pregnancy-related determinants are responsible for occurrence of CH, which should be investigated through more complex statistical analysis.

Conflict of interest: Authors have no conflict of interest.

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