Review Article:

A Systematic Review on the 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.

Objective: We aimed to review the reported CH-related risk factors systematically.

Data Sources: In this review, all types of human studies on the risk factors related to the occurrence or high rate of CH were included. An electronic search was conducted in international and national electronic databases. The following keywords were used: "Congenital Hypothyroidism" AND "risk factor".

Study Selection: In this review, 373 papers (from PubMed: 199; Scopus: 36; ISI: 53, SID: 55, Ovid: 11; Science Direct: 19) were identified through electronic database search. A total of 98 articles were assessed for their eligibility, from which 60 qualified articles were selected for final evaluation. Most of the studies have cross-sectional, case-control, and prospective design.

Data Extraction: The current review was conducted and reported following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement.

Results: Reported risk factors for transient CH were as follows; iodine deficiency and excess, prematurity, advanced 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 the thyroid gland were as follows; female gender, familial history of CH, birth in geographical areas with a high rate of the disease, advanced maternal age, ethnicity (Caucasians), but not seasonality. Reported risk factors for permanent CH with dyshormonogenesis were a familial history of CH and origin of both parents from the high-risk geographical region.

Conclusions: By using this information, 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. Also, for risk factors with limited evidence, more studies should be performed.

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1. Context

Congenital Hypothyroidism (CH) is the most common endocrine disorder and causes of preventable mental retardation in children. It is defined as thyroid hormone deficiency at birth (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 signs and symptoms at birth or during neonatal period. It is a routine practice in developed countries and many developing countries. Findings of CH screening from different regions and countries indicate great variability in the incidence and etiology of CH. In accordance with CH screening, etiological factors, and various risk factors of the disorder have been identified and reported in previous studies (3, 4).

Findings of the studies demonstrate 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. The investigation of modifiable risk factors for CH is important because of the potential to prevent CH, especially in regions with a high rate of CH.

Based on the current evidence, several individual and environmental factors affect 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 the occurrence of CH (5-12). Confirming the causality between these risk factors and CH and identifying them might be helpful even in decreasing the incidence of CH. More practically, it can help have a higher index of suspicion for CH in neonates with the identified risk factors.

2. Objective

Though there are different studies in this field, the results are not conclusive 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 research. So we aimed to review the reported CH-related risk factors systematically.

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 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, as well as Persian databases such as IranMedex, IranDoc, and Scientific Information Database (SID). The keywords of “congenital hypothyroidism” (Mesh) AND “risk factor” (Mesh) were used in the Title and the abstract. The latest search was conducted on the 29th September 2017.

4. Study Selection

In this review, all types of human studies on the risk factors related to the occurrence or high rate of CH were included without any time limitation. The included articles were in English and Persian. The search was performed without any time limitation until September 2017. Inappropriate or repeated papers were excluded. The titles of all searched articles were reviewed and studied, and repeated items were excluded. Two researchers carefully studied the full text of selected articles and excluded irrelevant papers. A secondary search was conducted from the references of the 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 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, mutual discussion, and consulting with an expert in the field of CH. From each finally included article, the following information was extracted; authors, place of the study, ethnicity, year of publication, sample size, study design, and reported risk factors.

In this review, 373 papers (PubMed: 199; Scopus: 36; ISI: 53, SID: 55, Ovid: 11; Science Direct: 19) were identified through electronic database search. A total of 98 articles were assessed for eligibility, of which 60 qualified articles were selected for final evaluation (Figure 1). Details of all selected studies were presented in Table 1 (5, 8, 9, 12-67).

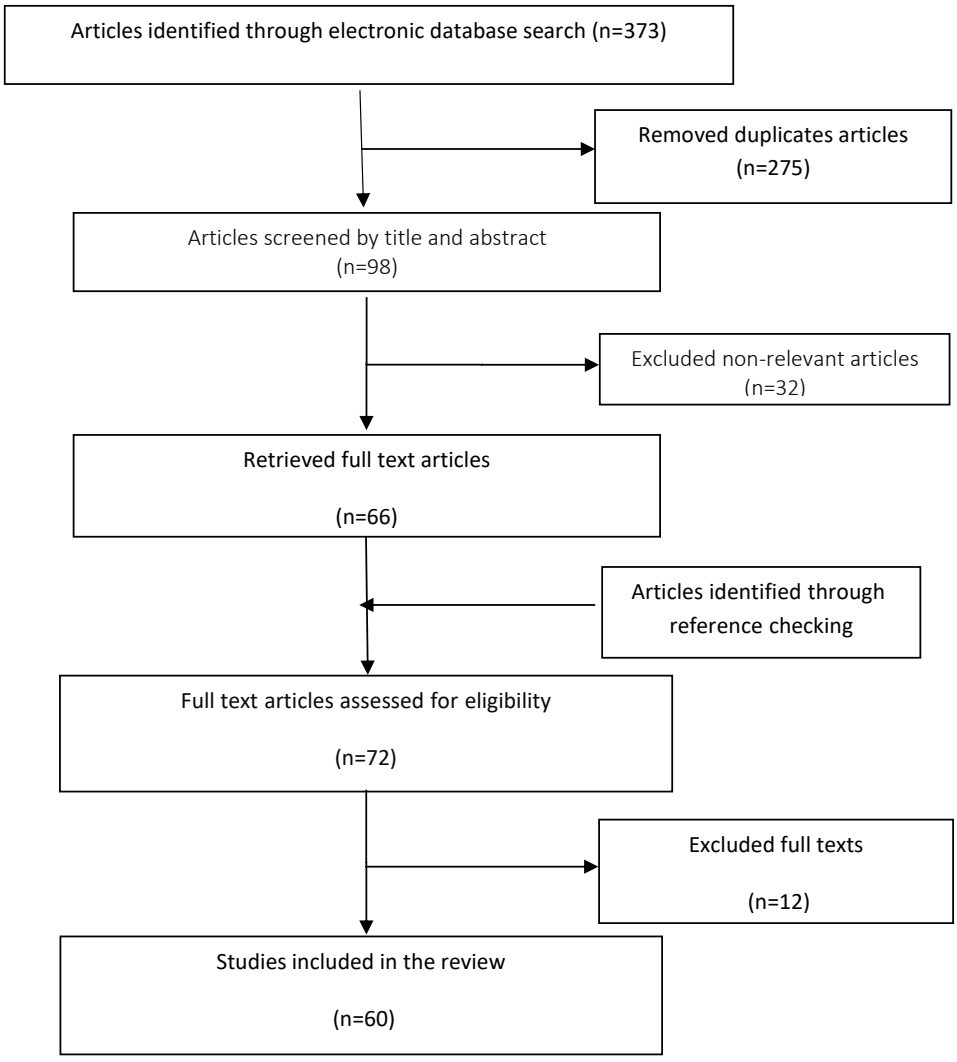

Figure 1. Flowchart of study selection

6. Results

Most of the studies have cross-sectional, case-control, and prospective design. Most of them evaluated the possible risk factors for primary CH. Reported risk factors for transient CH were as follows: iodine deficiency or excess, prematurity, old maternal age, male gender, retinopathy of prematurity, twin pregnancy, maternal autoimmune thyroid disease, intrauterine growth retardation, and cesarean delivery (19, 24, 26, 33, 51, 56, 63). Reported risk factors for permanent CH with dysgenesis of the thyroid gland were as follows: female gender, familial history of CH, birth in geographical areas with a high rate of the disease, old maternal age, ethnicity (Caucasians) but not seasonality (5, 15, 42, 50, 56, 61).

Reported risk factors for permanent CH with dyshormonogenesis were the familial history of CH and origin of both parents from the high-risk geographical region (15). In five papers, the effects of risk factors on the TSH level during screening were evaluated (14, 25, 28, 6, 33).

7. Discussion

In this review study, we studied all reported studies in the field of CH risk factors. Most of the reviewed studies were cross-sectional and evaluated the risk factors of primary CH. Few studies were investigating the risk factors of permanent vs. transient or different etiologies of CH. Though some of the reported risk factors for permanent and temporary CH and various etiologies of permanent CH were similar, some of them were specific for the mentioned groups. By considering the reported group differences, we could design more studies for better understand-

Table 1. Details of the papers

No.	Name of First Author, Year, Place	Sample Size	Type of Study	Type of CH	Reported Risk Factors
1	Thalhammer et al. Austria (13)	Results of CH screening since 1976	Cross-sectional	Permanent CH	Seasonality
2	Meberg A et al. Norway (14)	46 smoker and 49 nonsmoker mothers	Case-control	Serum TSH	Smoking mother
3	Rosenthal et al. England (69)	289697 screened neonates (from November 1981 to February 1987)	Cross-sectional	Primary CH	Parental consanguinity
3	Virtanen et al. Finland (15)	307000 screened neonates	Cross-sectional	Permanent CH	Female gender, CH in the family, high risk geographic region, seasonality for dysgenesis History of CH in the family and high risk geographic region for dyshormonogenesis
4	Kaiserman et al. Israel (16)	303 primary CH patients	Cross-sectional	Primary CH	-
5	Lorev et al. USA, California (17)	Over 5 million infants	Prospective	Primary CH	Female gender for all ethnic groups except blacks
6	Sorcini et al. Italy (18)	239 cases of CH	Prospective	Primary CH	Iodine deficiency
7	Dussault et al. Quebec, Canada (19)	259 mothers of CH newborns	Cross-sectional	Transient CH	Maternal autoimmune thyroid disease (antimicrosomal antibodies)
8	Hall et al., England (20)	1128632 neonates screened over 16 years	Cross-sectional	Primary CH	Season, Parental consanguinity
9	Waller et al. California,USA (12)	1806 cases of CH	Cross-sectional	Primary CH	Low-birth weight, macrosomia, ethnicity, gender
10	Rocchi et al. Italy (21)	92 CH patients	Retrospective	Primary CH	-
11	Henry et al. Saudi Arabia (22)	44 CH patients from 121404 screened neonates	Cross-sectional	Primary CH	-
12	Ordookhani et al. Tehran, Iran (23)	22 CH patients from 20107 screened neonates	Cross-sectional	Primary CH	Parental consanguinity
13	Buyukgebiz A, Turkey (24)	-	Review paper	Transient CH	Prematurity
14	Ouhoummane et al. Canada (25)	32978 screened newborns (1993-1999)	Retrospective	Primary CH	Chlorine dioxide (ClO_2) in disinfected water for Low-birth-weight infants
15	Ordookhani et al. Tehran, Iran (26)	41 CH patients (6 of them transient CH)	Cross-sectional	Transient CH	Exposure with iodinated disinfectants during the perinatal period
16	Lian et al. China (27)	35 CH patients	Retrospective	Primary CH	Prematurity, modest or massive hypertension during pregnancy, high serum anti-thyroid peroxidase antibodies levels
17	McElduff et al. Australia (28)	2031screened neonates	Cohort study	Primary CH	Cesarean delivery
18	Medda et al. Italy (6)	173 cases and 690 controls were enrolled in 4 years	Case-control	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. Québec, Canada (5)	424 CH patients	Cross-sectional	Permanent CH with dysgenesis	-

No.	Name of First Author, Year, Place	Sample Size	Type of Study	Type of CH	Reported Risk Factors
20	Ordookhani et al. Tehran, Iran (29)	48106 screened neonates	Cross-sectional	Serum TSH	Cesarean delivery
21	Hashemipour et al. Isfahan, Iran (30)	358 CH patients from 113282 screened neonates	Cross-sectional	Primary CH	The month of birth, suspected environmental factors
22	Gu et al. Japan (31)	1586 CH patients	Cross-sectional	Primary CH	Gender, season
23	Hashemipour et al. Isfahan, Iran (32)	274 CH patients	Retrospective	Primary CH	First cousin parental consanguinity
24	Olivieri et al. Italy (33)	3600 CH patients	Retrospective	Both transient and permanent CH	Twin birth, environmental factors
25	Mao et al. China (9)	289 CH patients	Cross-sectional	Primary CH	Post-term birth, low-birth-weight infants, macrosomia
26	Rowland et al. USA (34)	-	Clinical inquiries	Primary CH	Prematurity, infants wellbeing (cerebral pathology, low Apgar scores, respiratory distress syndrome, persistent ductus arteriosus requiring treatment, necrotizing enterocolitis), maternal thyroid disease, iodine deficiency/excess
27	Eftekhari et al. Kerman, Iran (35)	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 used by mothers
28	Sepandi et al. Shiraz, Iran (36)	126 CH patients and 401 controls	Case-control	Primary CH	Parental consanguinity, birth defects, birth defects in the first-degree relatives, female gender, twin births, prematurity
29	Cranston et al. California, USA (37)	698 CH patients	Cross-sectional	Primary CH	Prematurity, maternal age, civilian maternal status
30	Hashemipour et al. Isfahan, Iran (38)	68 CH and 178 healthy children and their mothers	Cross-sectional	Primary CH	Milk iodine concentration and iodine excess
31	Hinton et al. The USA (8)	142 CH patients from 47075 screened neonates	Cross-sectional	Primary CH	Race, ethnicity, sex, and pregnancy outcomes
32	Aminzadeh et al. Ahvaz, Iran (39)	142 CH patients from 47075 screened neonates	A prospective two-year study	Permanent CH	Season
33	Hashemipour et al. Isfahan, Iran (40)	194 CH and 350 normal and their first-degree relatives	Case-control	Primary CH	Hypothyroidism
34	Safar Alizade et al. Khoy, Iran (41)	16 CH patients	Prospective	Primary CH	Parental consanguinity, maternal diet during pregnancy (chicken)
35	Stoppa-Vaucher et al. Montréal, Canada (42)	190 patients with TD (147 ectopies, 40 athyreosis, and 3 hypoplasias) and the 44 patients with DH	Case-control	Permanent CH with Thyroid Dysgenesis (TD)	Ethnicity
36	Hashemipour et al. Isfahan, Iran (45)	65 patients with CH and their mothers as the case group and 148 healthy neonates and their mothers as the control group	Case-control	Primary CH	Maternal thyroid autoimmunity (Thyrotropin Receptor Antibodies [TRAb])
37	Zeinalzadeh et al. East Azerbaijan, Iran (44)	94 CH patients from 62,459 screened neonates	Cross-sectional	Primary CH	Maternal age
38	Ooki S.Japan (45)	18 CH patients	Retrospective	Primary CH	Multiple births
39	Abdelmoktader et al. Egypt (46)	320 cases and 320 controls 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

No.	Name of First Author, Year, Place	Sample Size	Type of Study	Type of CH	Reported Risk Factors
40	Rezaeian et al. Hamadan, Iran (47)	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. Liverpool, UK (48)	6498 neonates during CH screening	Retrospective	Primary CH	Low-birth weight
42	Dalili et al. Guilan, Iran (49)	221 CH patients from 119701 screened neonates	Retrospective	Primary CH	Low-birth weight, postdate delivery, macrosomia, vaginal delivery
43	Kirmızibekmez et al. Turkey (50)	234 CH patients	Retrospective	Permanent CH with dysgenesis	Maternal age
44	Rabbiosi et al. Italy (51)	84 CH patients and ectopic 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. Kordestan, Iran (52)	105 CH patients and 105 controls	Case-control study	Primary CH	Familial thyroid disease
46	Rezaeian et al. Hamadan, Iran (53)	277 cases (CH patients) and 1036 controls	Case-control	Primary CH	Interaction of gender (girl) and birth season (summer)
47	Dorreh et al. Arak, Iran (54)	414 CH patients from 127 112 screened neonates	Cross-sectional	Primary CH	Family history of thyroid diseases
48	Uenaka et al. Japan (55)	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. China (56)	1210 CH patients	Prospective	Transient CH	Iodine deficiency
50	Satoh et al. Japan (57)	212 infants born to mothers who become pregnant after undergoing hysterosalpingography involving the use of ethiodized oil	Prospective	Primary CH	Using ethiodized oil contrast medium during hysterosalpingography
51	Mehrnejat et al. Isfahan, Iran (58)	667 CH patients from 275485 screened neonates	Descriptive-analytic	Primary CH	Nitrate concentration in drinking-water
52	Zhou et al. China (59)	125 neonates with CH (case group) and 375 neonates without CH (control group)	Case-control	Primary CH	Mother's age, gestational diabetes, gestational thyroid disease, birth weight, gestational age, fetus number, fetal distress, birth defects
53	Trumpff et al. Brussels, Belgium (60)	313 Belgian mothers and their 4- to 5-year-old children	Retrospective cohort study	Primary CH	Season, maternal smoking, lower weight gain during pregnancy, gestational age
54	Dayal et al. India (61)	80 CH patients	Retrospective	Permanent CH (dysgenesis)	Maternal age
55	Keshavarzian et al. Shadegan, Iran (62)	203 CH patients and 657 controls	Case-control	Primary CH	Parental consanguinity, urbanization
56	Aguiar et al. Massachusetts, USA (63)	76	Retrospective	Transient vs. permanent CH	Maternal age, cesarean delivery, retinopathy of prematurity for transient CH
57	Blasig et al. Berlin, Germany (66)	84 CH patients	Cross-sectional	Primary CH	Serum Cu
58	Yang et al. 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. Macedonia (68)	46 CH patients	A 14-year retrospective cohort analysis	Primary CH	Ethnicity

No.	Name of First Author, Year, Place	Sample Size	Type of Study	Type of CH	Reported Risk Factors
60	Khanjani et al. Kerman, Iran (69)	773 CH patients from 288437 screened neonates	Cross-sectional	Primary CH	Season

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ing of different subgroups of CH. As mentioned previously, though there were studies regarding CH-related risk factors (6, 34, 36, 44, 47, 49, 56, 59, 63) there was no comprehensive review in this field. Moreover, for some important risk factors such as seasonality or gender differences, the results of studies were not in agreement. We classified the risk factors in the following categories; known risk factors with enough and appropriate evidence, known risk factors with controversial results, and risk factors with limited evidence which need more evaluations.

The role of some risk factors such as ethnicity, thyroid disorders in families, other birth defects, pre-term 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, 32, 33, 45, 48, 52, 54, 55, 62, 65, 66). Though there were also few studies which did not report such an association, almost all of them support the role of above-mentioned risk factors for CH. However, the additive effect of the risk factors for the occurrence of CH should be investigated in future research.

Iodine deficiency or excess (18, 26, 34), gender (31, 17), seasonality (5, 13, 20-22, 30, 67) maternal age (12, 37, 44, 61, 63), type of delivery (28, 62) and maternal anti-thyroid drug use (6, 27) were the risk factors with controversial reports. Though their role as CH-related risk factors has been demonstrated in previous studies, the findings are not conclusive.

Iodine deficiency is one of the most critical risk factors for CH, but by the elimination of iodine deficiency in different countries, it seems that iodine excess is considered as a risk factor for CH (18, 26, 34). 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 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 findings in 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 medium should be reduced to minimize the risk of thyroid dysfunction in fetus or neonates (57).

Previous studies showed an association between gender and CH. Many reports have indicated that CH is frequently found in girls (12, 15, 17, 6, 31, 36, 44, 46, 53, 56). According to previous studies, the female to male ratio was approximately 1.0 among hereditary cases of CH (31). Moreover, this ratio was about 2.0 for the CH cases with both athyreosis and ectopic groups (17). Castanet et al. reported that the female preponderance over males for isolated CH was similar to those with the ectopic thyroid gland or athyreosis (68). 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 (49).

Recently, Rezaeian et al. in Hamedan, Iran studied the potential interactions that could change the effect of gender on congenital hypothyroidism (53). 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 no significant difference between girls and boys regarding gestation and birth weight in all etiological subgroups such as athyreosis and ectopic groups (48). Rezaeian and colleagues have finally indicated that birth season might act as an interaction to increase the risk of CH in girls (53).

However, it is unclear why girls have a higher incidence rate of CH than boys, while there is no difference in the proportion of other risk factors between them. So, the reasons for gender differences deserve further investigations. The results of the reviewed literature regarding the seasonal relationship were inconsistent, too. Gu et al. in Japan reported that temperature and season had a significant effect on CH. According to them, from January to December, males and females had one and two peaks, respec-

tively (30). In the British Midland, higher incidence of CH was 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 Northwest of England, in Asian families compared with non-Asians (69). No evidence of seasonal variations was reported during the CH screening program in Saudi Arabia and Italy (21, 22). 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 incidence of CH had no significant periodicity (16).

There were different studies from Iran on this topic, too. Ordookhani et al. reported a significant correlation between winter and CH. Hashemipour et al. reported higher and lower incidence rates of CH in summer and the last month of autumn, respectively (16). Their 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 a 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 reported that the prevalence of CH had a significant negative correlation with temperature. The odds of being affected increased by 4% for each 1°C drop in temperature (39). Findings of other studies from Iran showed a 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 evaluated 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 the highest rate of CH in October (autumn) and lowest in June (summer) (67).

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 the incidence of CH in each region.

Some studies reported advanced maternal age as a risk factor for CH (12, 37, 44). But some of them have reported such an association only for thyroid dysgenesis (64). According to the documents, the maternal age of more than 35 years could be a risk factor for CH (47).

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 have also reported a higher incidence rate of CH in both emergency and elective cesarean sections (47). Whereas Ordookhani et al. reported that umbilical 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 (6).

Similarly, Dalili et al. have reported that the frequency of Normal Vaginal Delivery (NVD) was significantly higher in neonates with CH compared to the normal population (49). It seems that different conditions related to the type of delivery, including the iodine condition of the population, method of delivery and using different disinfectant have an 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 thyroid function of neonates (27, 55). Lian et al. in China 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 might be increased (26). 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, 58), dietary component of mothers during prenatal period (41, 64), neonatal jaundice (47), maternal anemia (48), intrauterine growth retardation (6), lower weight gain during pregnancy (60), urbanization (62), parental occupation and education (35, 47), gestational diabetes (6, 46, 59), and smoking (14, 47, 60) have limited evidence. It seems that more studies for investigating the association of the mentioned risk factors with CH are necessary. Of the above-mentioned risk factors, some have high priority, including environmental pollutants, smoking, gestational diabetes, and maternal anemia due to their effectiveness in preventative medicine.

So far, few studies have investigated the effect of environmental factors on CH incidence. Ouhoummane et al. in Cana-

da compared the thyroid function of newborns from 11 municipalities where drinking water was disinfected by Chlorine Dioxide (ClO_2) 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 ClO_2 were considered. However, for newborns with low-birth weight, mean TSH level was significantly higher among those exposed to ClO_2 than for those in the reference group. They concluded that ClO_2 was a risk factor for CH in preterm and low-birth-weight neonates (26). In another study in Iran, Mehrnejat et al. found no significant relationship between nitrate concentration in drinking water and the incidence of CH through linear regression analysis (58).

In two studies, the dietary component of mothers has been reported as risk factors for CH, including Cu deficiency and some other nutritional components (41, 64). It seems that evaluating the association of prenatal dietary components is helpful for identification of CH-related modifiable risk factors. The limitation of the current review was the heterogeneity of papers so that we could not do 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 the current review provide us basic information about reported CH-related risk factors from different countries. Using this information, we could plan more etiologic studies to investigate the pathogenesis of the disorder, design interventional studies for the known modifiable risk factors, and reduce the rate of CH in our region. Besides, for risk factors with limited evidence, more studies should be performed.

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

Ethical Considerations

Compliance with ethical guidelines

There are no ethical considerations to be noted in this article.

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Authors' contributions

All authors contributed in designing, running, and writing all parts of the research.

Conflicts of interest

The authors declare no conflict of interest.

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