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Prevalence of Congenital Hypothyroidism in Iranian Infants

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ABSTRACT

Background and Objective: Congenital hypothyroidism is one of the most common endocrine diseases and one of the main causes of mental disability and delayed sensory and motor development in infants. The aim of this review article is to determine the general prevalence of congenital hypothyroidism in Iranian infants.

Methods: In this systematic review and meta-analysis, a comprehensive review of the Scientific Information Database (SID), Medline (PubMed), ScienceDirect and Google Scholar was conducted using the keywords "congenital hypothyroidism", "infants" and "screening" until November 2022. The extracted data were entered into the Comprehensive meta-analysis software (Version 2) and the meta-analysis was analyzed using the random-effects model in the studies.

Findings: 248 articles were initially found in the search of the investigated databases. After removing 169 duplicate articles and removing them based on the inclusion and exclusion conditions of the studies, 79 articles were included in the secondary evaluation and finally, after omitting 60 irrelevant articles, 17 articles were included in the meta-analysis review. In a review of 17 studies with a sample size of 674,466 Iranian infants, based on a meta-analysis, the prevalence of congenital hypothyroidism in Iranian infants was 0.002 (95% CI= 0.002-0.003), and in terms of percentage was reported 0.2% and 2 per 1000 live births.

Conclusion: The results of the present study show that the prevalence of congenital hypothyroidism in Iranian infants is 2 per 1000 live births, which indicates the high prevalence of this disease in infants in the country, and it is necessary to inform pregnant mothers and to continue screening at birth.

Keywords: *Congenital Hypothyroidism, Infants, Screening*.

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Introduction

Congenital Hypothyroidism (CH) is one of the most important and common endocrine diseases and one of the main causes of mental disability and delayed sensory and motor development in infants and children. Although this disease causes severe mental disability in infants, it can be prevented with early diagnosis and treatment (1).

Thyroid hormone is very important for neurological growth and development, especially in the early years of life of infants, and hypothyroidism during this period of infancy is one of the most important causes of preventable mental disability in Iran and all over the world (2).

CH can be diagnosed either as transient or permanent; transient types of congenital hypofunction of the thyroid gland are prevalent in areas with moderate to severe iodine deficiency (1-3). The permanent type has been reported as the most common type of congenital hypothyroidism in infants, and the most common congenital disorder in the body's endocrine system. The highest percentage of causes of permanent congenital hypofunction of the thyroid gland is sporadic and caused by the developmental disorder of the thyroid gland known as thyroid dysgenesis (1-3).

CH can be caused by various factors, such as thyroid agenesis, insufficient (hypoplastic) development, and gene mutation that disrupts the synthesis of thyroid hormones. These influential factors that cause congenital hypothyroidism are detected through infant screening (3).

This disease has no specific symptoms or has very mild symptoms in the first weeks of the disease and is diagnosed only through primary screening or laboratory methods (4). The studies conducted regarding CH have reported the prevalence of this disease in infants differently. Some studies have considered its prevalence to be between 1 per 2000 to 1 per 4000 live births (5).

Studies have reported that the prevalence of CH in Asian race is higher than other races and the prevalence of this complication in Iran is also higher than other countries (6). The prevalence of hypothyroidism is 1 per 16,000 live births in Egypt (7), 1 per 3,000 live births in New Zealand (8), and 2 per 1,000 live births in Iran (9).

The reasons for the diversity of reports in different studies in the world can be due to issues such as the difference in conventional criteria that are considered for the definitive diagnosis of hypothyroidism in infants. In addition, ethnic and racial differences and high consumption of iodine-containing antiseptics, especially in premature infants, are among the causes of the prevalence of transient hypothyroidism (10-12), which seems to be more prevalent in Iran compared to other countries. However, it should be noted that many hypothyroid infants have a normal appearance and their clinical symptoms at birth are few and non-specific (13).

The CH screening program is important both in terms of preserving the potential spiritual capital of the society and from the material and economic point of view, because the cost of maintaining and treating sick infants and children and the complications caused by hypothyroidism and mental retardation are estimated to be far more than the cost of screening (13, 14). Despite various advantages of screening and preventing severe effects caused by hypothyroidism in infants and reducing the high costs of treatment in affected infants, screening in most countries of the world has weaknesses. Various studies relate the main cause of these problems to the method of collecting blood from the heel and people's non-cooperation and state that since the appropriate time for screening is 72 hours after the birth of an infant, some families will not return for screening (15).

In a study conducted in Mazandaran, the prevalence of congenital hypothyroidism in infants was reported to be 1.6 per 1000 live births (16), in a study in South Khorasan, 1.8 per 1000 live births (17), in a study in the south of Kerman, 7.4 per 1000 live births (18), and in a study conducted in Mashhad, 2.6 per 1000 live

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births (19). Considering the importance of congenital diseases in children, reducing the complications of these diseases in children and also preventing the high costs of treatment caused by congenital diseases, especially congenital hypothyroidism, and considering that effective screening in this area is also done in the country, but as mentioned before, the studies conducted in Iran demonstrated different results regarding the prevalence of congenital hypothyroidism in infants in different regions of the country, this systematic review and meta-analysis was conducted to investigate the overall prevalence of congenital hypothyroidism in Iranian infants in order to guide health policymakers in this field to investigate the effect of educational, screening, diagnostic and treatment methods in congenital hypothyroidism in Iranian infants.

Methods

In this systematic review and meta-analysis, a systematic search of the investigated databases was performed according to the criteria of the PRISMA statement and diagram. Systematic search of articles was done in PubMed, ScienceDirect, SID and Google scholar databases and the keywords used for searching in this study were selected based on published primary studies as well as MESH Terms. The keywords used in this study included congenital hypothyroidism, infant, infant screening, TSH, T4 and thyroxine. Also, to combine keywords, AND and OR operators were also used in the advanced search of the mentioned databases. The search in these databases was done without time limit and until December 2022.

In this review, descriptive and observational studies (case-control and cohort) that emphasized the prevalence of congenital hypothyroidism in Iranian infants, as well as studies that examined hereditary hypothyroidism in infants based on the THS and T4 criteria were included in the study, and studies that investigated hypothyroidism (values higher than the normal range of TSH) in non-infants, case studies, clinical trials, systematic reviews and meta-analyses were excluded from the study.

The searched studies were entered into the EndNote software, and after removing duplicates and studies unrelated to the subject of the review, the quality of the studies was assessed by the authors based on the inclusion and exclusion criteria. The evaluations in this study were done independently and in a blinded way by three researchers. For this purpose, a list of articles without mentioning the title of the study as well as the authors was provided to the researchers so that the investigations could be carried out. At first, two authors separately examined the title and abstract of the articles according to the inclusion criteria, and if there was a disagreement between the two researchers, the third researcher's final opinion was considered.

The quality of observational studies was evaluated by STROBE checklist. This checklist examines various aspects of writing an observational and descriptive study (15). This checklist has 32 different items and the range of scores varies between 0-32. In this study, the articles that received a score of 16 and above in the evaluation of the quality of studies by the STROBE checklist were included in the study as high-quality studies.

Finally, after the extraction of the desired articles, the data of these studies were entered into the Comprehensive Meta-analysis (CMA, Version 2) software and the heterogeneity of the studies was analyzed using I^2 test and then the random effects method was used to analyze the results. The publication bias in the studies was assessed by Egger test, and in order to check the effective factors in creating heterogeneity in the studies, the meta-regression test was used in two variables of sample size and the year of the study.

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Results

After searching the databases in this study, 49 articles were found in the PubMed database, 33 articles in the ScienceDirect database, 115 articles in the Google Scholar database, and 51 articles in the SID database, and finally, 248 articles were initially found in all the reviewed databases. After finding 169 duplicate articles and omitting them based on the inclusion and exclusion criteria of studies, 79 articles entered the secondary assessment. After omitting 60 unrelated articles and articles without sufficient information, 17 articles were included in the meta-analysis (Figure 1 and Table 1).

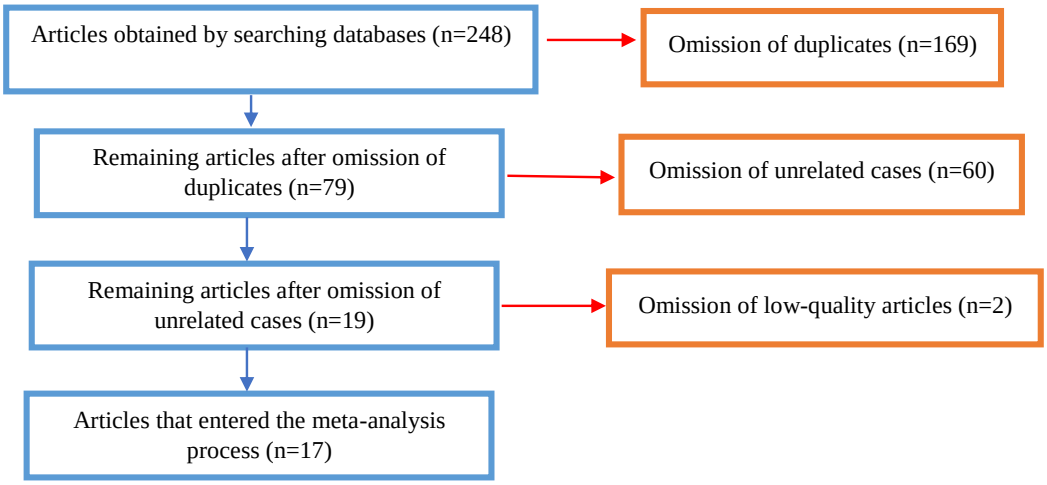

Figure 1. Steps of including, evaluating and screening the studies in the systematic review based on the PRISMA model

Table 1. Data extracted from the reviewed studies

Row	First author	Publication year	Location	Number	Prevalence (in 1000 live births)	STROBE score
1	Âkha O (16)	2011	Mazandaran	45218	1.6	22
2	Namakin K (17)	2012	southern Khorasan	38987	1.8	20
3	Amiri F (18)	2019	south of Kerman province	4999	7.4	24
4	Peikani S (19)	2018	Mashhad	4484	2.6	20
5	Ordookhani A (20)	2004	Tehran and Damavand	35067	0.9	18
6	Zamani N (21)	2019	Borujerd	13741	1.6	22
7	Abedi M (22)	2014	Sanandaj	39162	3.8	19
8	Mohammadi E (23)	2012	Kerman	48277	3.4	19
9	Hashemipour M (24)	2004	Kashan	3005	3.3	20
10	Nele S (25)	2010	Kurdistan	24806	4.9	20
11	Dorreh F (26)	2010	Arak	25685	3.3	21
12	Kalantari S (27)	2004	Rasht	3000	0.6	18
13	Hashemipour M (28)	2004	Esfahan	20000	2.7	23
14	Eftekhari N (29)	2008	Kerman	3000	1	19
15	Saffari F (30)	2008	Qazvin	33488	2.2	20
16	Zeinalzadeh AH (31)	2011	East Azarbaijan	62459	1.5	21
17	Beheshti Z (32)	2014	Mazandaran	269088	2	23

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In the review of 17 studies with a sample size of 674,466 infants, the I^2 heterogeneity test showed high heterogeneity (I^2=93.9), and accordingly, the random effects method was used to analyze the results. Therefore, based on the meta-analysis, the prevalence of congenital hypothyroidism in Iranian infants was 0.002 (95% CI= 0.002-0.003), which was reported as a percentage of 0.2 and 2 per 1000 live births (Figure 2). The highest prevalence of congenital hypothyroidism was in a study by Amiri et al. in 2018 in infants from the south of Kerman with a prevalence of 0.7% (18) and the lowest prevalence of congenital hypothyroidism was in a study by Kalantari in 2013 in infants from Rasht with a prevalence of 0.06% (27). Furthermore, evaluation of publication bias in the studies through the Egger test shows the absence of publication bias in the studies (p=0.959) (Figure 3).

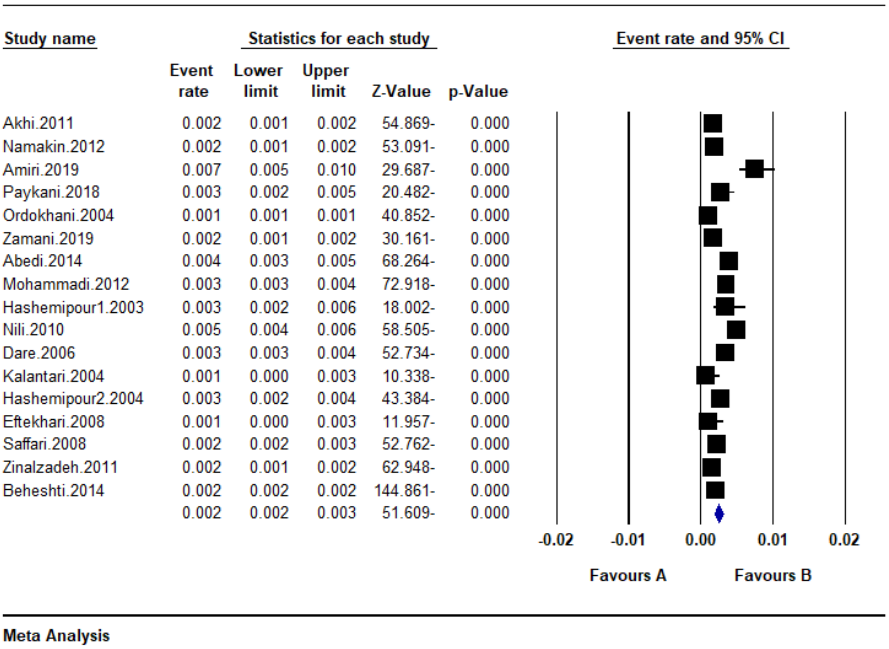

Figure 2. Forest plot of the prevalence of congenital hypothyroidism in Iranian infants based on the random effects method

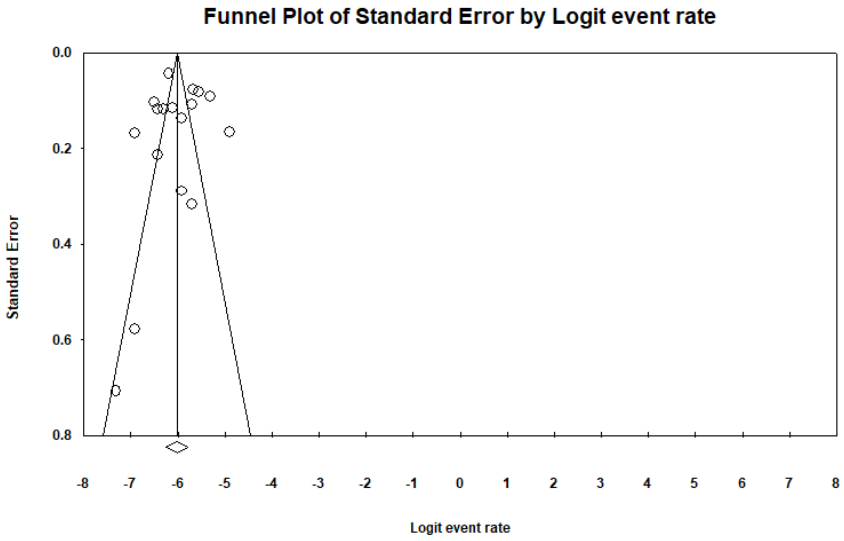

Figure 3. Funnel plot of the publication bias in the reviewed studies

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In examining the factors affecting the heterogeneity of studies and examining the effect of sample size on this heterogeneity, it was reported that with increase in sample size, the prevalence of congenital hypothyroidism in Iranian infants decreases, which was statistically significant ($p<0.05$) (Figure 4). In addition, with the increase in the year of conducting studies, the prevalence of congenital hypothyroidism in Iranian infants increases, which was not statistically significant ($p=0.248$) (Figure 5).

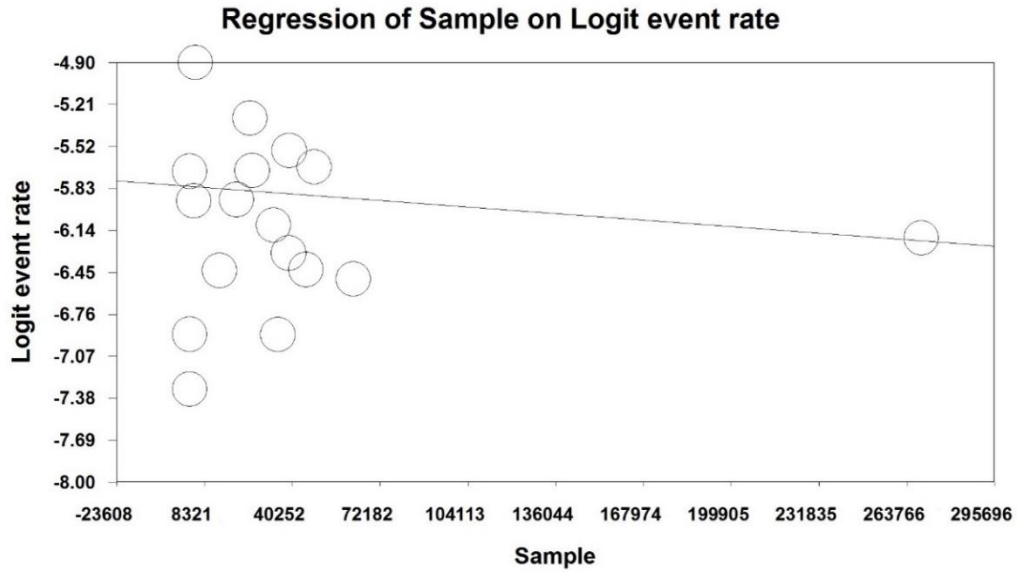

Figure 4. Meta-regression of the effect of sample size on the prevalence of congenital hypothyroidism in Iranian infants

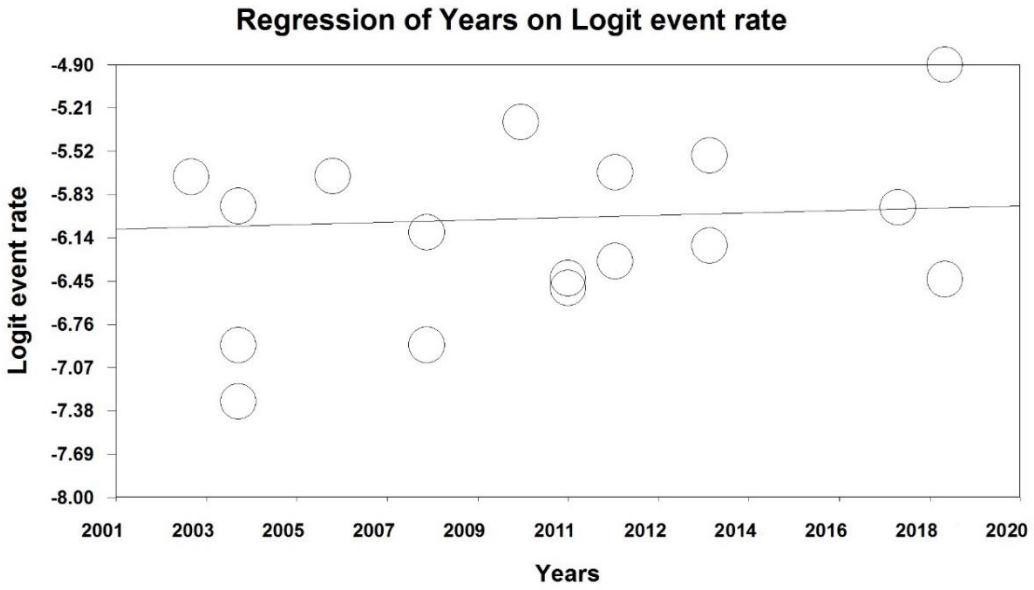

Figure 5. Meta-regression of the effect of the year of studies on the prevalence of congenital hypothyroidism in Iranian infants

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Discussion

According to the meta-analysis, the prevalence of congenital hypothyroidism in Iranian infants was reported to be 2 per 1000 live births. The figures reported in different regions of the world show different levels of prevalence, which shows the influence of climatic and racial conditions in addition to the impact of the living environment (30-32). A study conducted in Nigeria showed a prevalence of 1.67 in infants, a study conducted in Pakistan showed a prevalence of 1.781 in infants, and a study conducted in some parts of Asia showed a prevalence of 1.918 infants, and 1 in 10,000 infants was reported in African Americans (16). Furthermore, a study conducted in Egypt showed the prevalence of hypothyroidism as 1 in 16,000 live births (33), and a study conducted in New Zealand reported 1 in 3,000 live births (34), and in a study conducted in Turkey, the prevalence was 0.4 per 1,000 live births (35). Another study conducted in USA shows an increase in the prevalence of congenital hypothyroidism from 1 in every 3000 live births to 1 in every 2000 live births (36), while in European countries the reported prevalence varies from 1 per every 1000 to 1 per 10,000 (37).

The high prevalence of hypothyroidism can be due to iodine deficiency, genetic problems, problems caused by autoimmune diseases, and agricultural toxins (38, 39). In addition, different reports in different regions can be related to factors such as the use of T4 test with TSH alone for screening, determination of contractual criteria to diagnose hypothyroidism, as mentioned before, ethnic and racial differences, and environmental and hereditary factors (16).

Screening through laboratory methods, which is usually done in the first 3 to 5 days of birth by measuring TSH or T4 in a drop of dried blood from the infant's heel on filter paper, is the most important way to diagnose congenital hypothyroidism in infants (40). Another possible reason for the increase in each region can be the change of measurement methods and the change of sensitivity and specificity as well as the accuracy of diagnostic methods (19).

Moreover, the difference between the reports in Iran and other countries can also be due to the determination of the TSH diagnostic limit above 5 mlU/L by the Ministry of Health and Medical Education to diagnose hypothyroidism, which leads to reports with higher figures than the actual number of hypothyroidism cases (41), while TSH above 10 mlU/L is considered as the typical limit in screening for hypothyroidism in infants (16).

Various studies have reported that low birth weight is one of the most important influencing factors in newborns suffering from congenital hypothyroidism (42, 43). These studies have reported that the prevalence of hypothyroidism in low birth weight infants was more than 14 times that of normal weight infants (42). Several studies have also shown that the prevalence of hypothyroidism is very high in preterm infants and low birth weight infants, and transient neurological dysfunction is common in these infants, and early treatment can prevent the occurrence of disorders in them (44, 45).

Other studies have also reported that there is an effective and significant relationship between infant hypothyroidism and infant feeding with milk powder (46). Breast milk has a high concentration of iodine and thyroid hormones, and therefore it can be said that infants who are breastfed have a much lower chance of hypothyroidism than infants who are fed with milk powder (46).

Congenital hypothyroidism is one of the preventable causes of mental disorders in newborns, which can be prevented through effective screening methods, improved knowledge in families, and also providing adequate funds to prevent serious problems and irreversible complications in newborns, such as premature death of newborns. This can also prevent congenital abnormalities in infants and should be carefully considered by health policymakers to ensure the health of infants and also to provide a healthy young population.

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The results of the present study show that the prevalence of congenital hypothyroidism in Iranian infants is 2 per 1000 live births, and it indicates the high prevalence of this disease in the country's infants, and it is necessary to inform pregnant mothers of the complications and irreparable damage of this disease in children, and it is necessary to continue screening at birth and serious attention of health policymakers is required to reach lower levels of the prevalence of congenital hypothyroidism in infants in the country.

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