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Original Article

Risk Factors Related to Congenital Hypothyroidism: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Congenital endocrine disorders have a global impact on the morbidity and mortality of children and are a public health problem that heavily affects society and the daily lives of affected children and their families. The severity and consequences of congenital hypothyroidism (CH) on physical and especially cerebral maturation combined with lifetime mental retardation make CH neonatal screening one of the costliest preventive health programs. Thus, early diagnosis can improve the prognosis of the disease. The objective of the study is to examine CH's risk factors reported in previous studies.
Methods: Systematic review was performed according to the PRISMA checklist. PUBMED, Google Scholar, Scopus, MEDLINE, Web of Science, and Springer were analyzed using R version 4.0.3. For further review, we assessed eligibility analysis to identify influential studies.
Results: Of 63 studies, 21 studies were suitable for synthesis. Based on this review, risk factors related to CH were birth weight, age of pregnancy, female sex, home environment, notion of inbreeding, seasonality, multiple pregnancy, gestational diabetes, parity, advanced maternal age, parental thyroid disease, gestational diabetes, ethnicity, maternal body mass index (BMI), and socio-economic status.
Conclusion: This systematic review indicates that the risk factors related to CH vary by country and even by inter-region according to geographical, genetic, and socioeconomic specificities.

Introduction

Owing to the development and emergence of mass spectrometry and molecular biology techniques, more than 50 pathologies are currently being detected. Many international screening programs include five rare diseases: phenylketonuria, congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia, and sickle cell anemia. These programs have largely contributed to the prevention of irreversible disabilities in newborns and have improved their quality of life.[1]

Hypothyroidism is defined as insufficient production of thyroid hormones by the thyroid gland due to a hypo-metabolic state. It can be congenital, acquired permanently or temporarily, anatomical or functional thyroid,

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or central hypothalamic-pituitary.[2]

Newborn screening for congenital hypothyroidism (CH) is one of the most important advances in preventive medicine and child health in the 20th century. It prevents irreversible mental retardation in children through rapid diagnosis, early and adequate alternative treatment, and regular and rigorous medical follow-up.[3]

Forty-eight percent of children clinically diagnosed with CH had an intelligence quotient below 70 and psychomotor deficits in fine motor control and learning disabilities, in addition to a growth deficit in stature-weight.[4]

However, prior to the introduction of the CH neonatal screening program, there was an underestimation of the incidence of the disease due to the under-reporting of all cases that were not reported.[3] This loss of chance of diagnosis and consequently of therapy that results, unfortunately, generates a picture of severe mental debility. The disease is then only diagnosed at a late stage where the clinical picture is dramatic and the consequences are irreversible. This situation justifies the major interest in carrying out epidemiological studies on the etiologies and risk factors related to CH and on the other hand, to introduce systematic screening in all new-born and ipso facto, an early dose treatment adopted in the first two weeks of life to allow the child to develop all his intellectual potential.[5]

Despite the presence of various CH studies, the results remain inconclusive. Our goal is to conduct a systematic review of the risk factors related to CH to gather more obvious information to notify future research.

Methods

The study begins with a systematic review of the literature following a rigorous methodology to identify, select, evaluate and synthesize all relevant studies related to our specific research question according to the PRISMA approach. To do this, a thorough exploration of the main bibliographic databases - namely PubMed, Google Scholar, SCOPUS, Med Line, Web of Science and Springer was carried out using carefully adapted search algorithms, highlighting the key words "congenital hypothyroidism", "risk factors", "neonatal screening" and "epidemiological studies". This rigorous and comprehensive approach will allow us to base our analysis on a solid documentary basis, guaranteeing a thorough and nuanced treatment of this complex theme.

For our research, we defined inclusion and exclusion criteria to select relevant articles. Inclusion criteria included studies and articles containing the keywords of our research, with a limitation to publications in English and French. In addition, these criteria took into account the study design, participant characteristics and relevant outcome measures, thus ensuring that the selected articles were not only linguistically appropriate, but also methodologically robust. On the other hand, the exclusion criteria targeted studies that did not provide the information necessary to achieve our research objective. This included factors such as the quality of the study, completeness of data and type of article. Thus, of the 63 articles identified in the databases, we applied the criteria to select only those that met our requirements, thereby enhancing the clarity and rigor of our methodology.

Two independent reviewers were involved

in the study selection process, ensuring objectivity and rigor of the analysis. They have also been involved in resolving conflicts that have arisen during the review of articles. This approach has increased the transparency of our methodology. Their collaboration ensured a consistent and impartial evaluation of the selected studies.

To do this, of the 63 articles identified through the aforementioned databases, 22 articles (20 English articles and 02 French articles) were evaluated for their eligibility including 5 from PubMed, 5 from Google Scholar, 4 from SCOPUS, 4 from Med Line, 2 from Web of science and 2 from Springer. (Fig.1) This rigorous and comprehensive approach has allowed us to base our analysis on a solid documentary basis, guaranteeing a thorough and nuanced treatment of this complex theme.

After identifying the primary studies, the authors conducted a quantitative synthesis of the results of these studies in order to combine statistically the effects observed in the different studies, to obtain a more accurate estimate of the average effect of a risk factor by taking into account the quality and variability of the studies included.

This combined approach significantly strengthens the reliability and validity of the conclusions reached, making them a solid foundation for guiding clinical decision-making or developing recommendations for good practice.

Data Synthesis and Analysis

Data analysis consisted of an exercise in organizing and structuring the notes, aiming to bring out converging ideas, confront divergent perspectives, and then draw substantiated conclusions. The results are presented in a fluid and detailed text, enhanced by synthetic tables, thus offering a complete and thorough overview of the state of knowledge on this subject.

Results

The results of the operation of the articles selected for this systematic review are presented in the table below (Table 1).

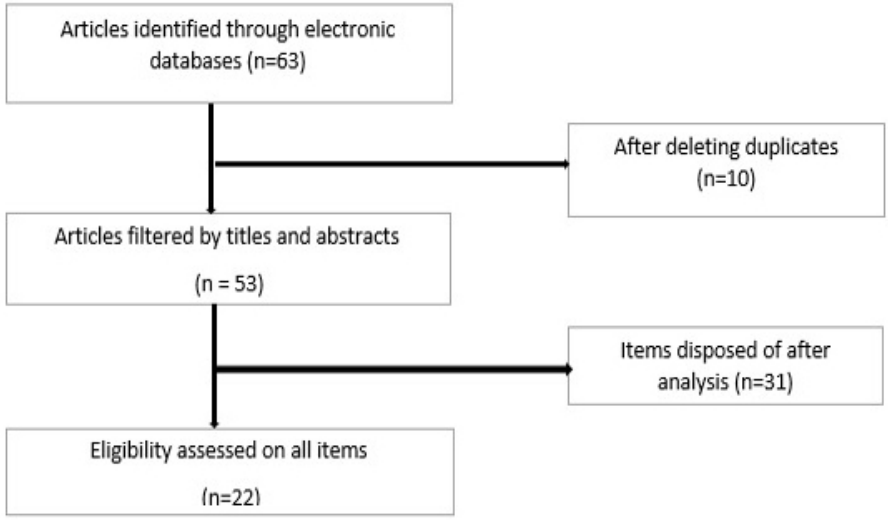

Figure 1. Organization chart of the research strategy according to the PRISMA guidelines

Table 1. Summary table of the results of the identified studies

Name of 1st author, place, and year of study	Type of Study	Size of the sample	Incidence rate	Risk factors
Zhou and al, China Fujian Region 2000-2018[6]	Retrospective Cohort	205 834 newborns	1/1089 Live-birth	-Low birth weight -Prematurity - Gestational diabetes, - Maternal hyperthyroïdism - Thyroïde dysgenesis
Zhang and al, China, Tianjin region, April 2015 to May 2017[7]	Prospective Cohort	988 pregnant women and their newborns	-	- Maternal age - Maternal Body mass index - The age of pregnancy - parity - Weight at birth
Ashrafalsadat Hakim, Iran, South West Region 2008-2020[8]	Transversal	350 children with congenital hypothyroidism	-	- Male sex - Prematurity -Urban environment - Notion of inbreeding - Parental thyroid disease - Ethnicity - Low birth weight
Dalili and al, Iran, Guilan Province, 2006-2007[9]	-	28904 newborns	1/781 Live-birth	- Low birth weight - Macrosomia - Prolonged pregnancy
Doustmahamadian and al, Iran, Semnan, 2011-2016[10]	Retrospective	17,507 Newborns	1/165 Live-birth	- Parity - Birth weight - Parental thyroid disease -Social level
Abbasi and al, Israël 2011-2015[11]	Retrospective	889,033 newborns	1/1024 Live-birth	- Female sex - The gestational age - Low birth weight - Winter births
Abdelmoktader, Egypt Fayoum Governorate, 2003-2010[12]	Control case	320 cases and 320 witnesses	-	- Female sex - Prolonged gestational age - Multiple pregnancy - Gestational diabetes
Marr and al, Canada, Ontario 2006-2015[13]	Cohort Retrospective	469 newborns screened for congenital hypothyroidism	-	- Female sex - Prolonged gestational age - Low birth weight
Maniar, and al Maroc, Fès,2001-2003[14]	Retrospective	156015 newborns	1/1952 Live-birth	-Female sex
Hall and al, England, 1987- 1997[15]	Transversal	1128632 newborns	1/2924 Live-birth	- Seasonality - Notion of inbreeding
Waller and al, USA, California, 1990-1998[16]	Transversal	5,049,185 newborns	1/2795 Live-birth	- Macrosomia - Low birth weight - Female sex - Ethnicity
Medda and al, Italy, 1997-2003[17]	Control case	173 cases and 690 witnesses	-	-Multiple pregnancy - Female sex - Prolonged gestational age -Family history of thyroid disease - Gestational diabetes
Kirmizibekmez and al, Turkey, 2008-2010[18]	Retrospective	234 cases	-	-Advanced maternal age

The selected studies were retrospective, cross-sectional, and prospective studies. They show that the prevalence of CH appears to be increasing in several countries due to many risk factors involved in the development of this pathology. The most cited risk factors concerned low birth weight,[6,7,8,9,11,17] female sex,[11,12,16,17] prolonged pregnancy,[9,12,17] gestational diabetes,[6,12,18] and parental thyroid disease history.[8,10,17]

we also note other less frequent tells that inbreeding,[8,15] prematurity,[6,8] ethnicity and advanced maternal age,[8,16] macrosomia,[9,16] multiple pregnancies,[12,17] parity,[7,10] seasonality,[15] urban living environment,[8] body mass index (BMI), social level of parents,[7] dysgenesis and maternal hypothyroidism.[6]

Discussion

In this systematic review, we inspected several articles on the risk factors related to CH. One of the strengths of this review is the diversity of research methods used in the various articles included, which enriches the results and allows a more complete view of the various risk factors studied.

Studies have pointed out that the correlation is significant between prolonged pregnancy,[9 ,12, 18] gestational diabetes,[6, 12, 17] parental thyroid history,[8, 10, 17] and CH screening.

A study in southwestern Iran examined the association between seasonal temperature variations and HC prevalence, but no significant correlation was found.[8] In contrast, other studies in Israel[11] and England[15] showed a higher incidence of CH in autumn and winter. In Morocco, the study conducted by Maniar et al[15] confirms what has been reported in terms of female predominance (75%) and the absence of seasonal influence. According to the same source, the incidence of CH in Morocco is 1/1952. This frequency is higher than in most developed countries where iodine deficiency has been corrected for a long time. Indeed, regardless of the continent, the incidence of CH varies between 1/3500 and 1/4000 19. This incidence is similar to that reported in studies in countries with moderate iodine deficiency, such as Turkey 1/2736 20 and Tunisia 1/2000. [21]

On the other hand, in the Tianjin region of China, where iodine intake is considered adequate, a study found a slight iodine deficiency in pregnant women. Variation in maternal thyroid hormones during pregnancy has been observed to influence the development of fetal thyroid and thyroid function in infants. The same study indicated that the mother's BMI, age, length of pregnancy, and parity were also risk factors associated with the likelihood of giving birth to a child with a TSH rate above 5 mUI/L[7].

The results of the vast majority of studies provide information on the role of perinatal factors in the cause and treatment of CH, hence the interest in considering them when diagnosing and treating CH.

In future studies, it would be necessary to explore and investigate other potential causes of CH, such as environmental factors and epigenetic characteristics. These investigations will deepen our understanding of the pathogenesis of CH.

In addition, some important social determinants such as the father's profession and education are significantly associated with the emergence of CH.[10] In the southwestern region of Iran, the vast majority of children with CH live in urban areas and half of the parents of children with CH have inbreeding relationships. To this end,

it is crucial to pay particular attention to these factors in healthcare programs to improve the effectiveness of CH prevention measures.[8]

However, patients with CH diagnosed with neonatal screening and treated had normal growth as a general population, indicating an effective screening program and treatment in this area.[9]

By analyzing these studies, we have been able to identify and synthesize the results, allowing us to better understand the determinants of CH and provide a solid foundation for appropriate health policy and interventions. This systematic review helps to consolidate knowledge in the field of CH-related risk factors by aggregating and rigorously analyzing existing studies.

By highlighting the irreversible consequences of CH, including mental retardation, we emphasize the importance of prevention and elimination of this condition. Health decision-makers will be able to consider these consequences when planning health policies and programs, ensuring that adequate measures are taken to reduce the prevalence of CH and minimize negative impacts on the cognitive and overall development of affected children.

Regular and consistent educational programs are essential to educate and educate parents about CH and its complications, with an emphasis on the importance of early detection, appropriate treatment, and regular follow-up. This will improve their knowledge and understanding, especially during pregnancy and after the birth of a child, and encourage appropriate management of CH.

Ultimately, this systematic review served to corroborate knowledge of CH's risk factors and to highlight current research gaps. It emphasizes the importance of prevention, education, and regular monitoring to reduce the negative consequences of CH, especially cognitive and developmental. To this end, it would be advisable for health policymakers to integrate these results into their policies and programs to improve the management of CH and ensure appropriate care for the children concerned.

Suggestions

To fill data gaps on CH risk factors, several research avenues are suggested. Multi-center epidemiological studies on diverse populations would be useful to better grasp prevalence and associated risks. The exploration of genetic and epigenetic factors, as well as the impact of environmental factors such as pollutants and nutritional deficiencies, is also crucial.

In addition, the role of family history should be examined and long-term follow-up studies conducted for children diagnosed. Finally, assessing the effectiveness of awareness and early detection programs could improve diagnosis and management. These approaches would significantly contribute to the understanding and management of this condition.

Conclusion

Through this systematic review, we were able to examine the current gaps in CH research and highlight the need for more studies to deepen our understanding of CH. The researchers stress the importance of better understanding the underlying mechanisms of the identified risk factors, evaluating the effectiveness of preventive interventions, and developing earlier and more effective screening approaches.

Empirical research on the epidemiology of CH

is crucial to identify risk factors associated with this disease and propose interventions and policies based on sound scientific evidence. One of the objectives of this review is therefore to clarify the challenges and issues of epidemiological research related to CH, to contribute to a better understanding of the disease and its public health implications.
Focusing on scientific evidence, this review will help inform health decision-makers on preventive measures and appropriate policies to address CH to reduce its prevalence and minimize its adverse consequences on infant health and further development.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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