Review Paper

Prevalence and Associated Risk Factors of Neonatal Hypoglycemia in Iran: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Neonatal hypoglycemia is the most common metabolic abnormality affecting newborns and contributes to increased morbidity and mortality.

Objectives: The present systematic review and meta-analysis aim to explore the prevalence and risk factors associated with neonatal hypoglycemia in Iran.

Methods: A systematic search was performed in Iranian and international databases, including SID, MagIran, Barakat Knowledge Network System, PubMed, Scopus, Web of Science, and the Google Scholar search engine searched for relevant articles using valid keywords. The search process was updated until September 28, 2021. Data were analyzed using STATA software, version 14, and the significance level for all tests was considered $P<0.05$.

Results: In 14 reviewed articles with a sample size of 18217, the prevalence of hypoglycemia in Iranian newborns was 29% [95%CI: 21%, 37%, P=0.0001] (64% in boys and 37% in girls). The hypoglycemia prevalence was 67% in infants born via cesarean section compared to 24% in vaginally delivered infants. The lowest and highest prevalence of neonatal hypoglycemia was observed in Mashhad (12%) and Arak (53%), respectively. The most common risk factors for neonatal hypoglycemia in Iran were infant prematurity (61%), septicemia (45%), respiratory distress syndrome (RDS) (26%), small for gestational age (SGA) (26%), maternal diabetes (21%), hypocalcemia (19%), intrauterine growth restriction (IUGR) (9%) and perinatal asphyxia (8%).

Conclusion: Neonatal hypoglycemia is very common in Iran, affecting nearly one-third of Iranian newborns. The prevalence of hypoglycemia in boys was almost twice as high as that in girls and 2.5 times higher in infants born by cesarean section than in infants delivered vaginally. Furthermore, prematurity was reportedly the most common risk factor for neonatal hypoglycemia in Iran.

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Introduction

The random glucose level in normal neonates falls by 25-30 mg/dL and may reduce to 55-60 mg/dL in the first three hours of life. The glucose level rises continuously during the first few days of life via various adaptation mechanisms. However, failure in this adaptation will lead to hypoglycemia [1, 2]. Neonatal hypoglycemia is considered a pediatric emergency, and lack of timely diagnosis and treatment leads to long-term adverse consequences, including mental retardation and seizures. Hence, early diagnosis and even screening of at-risk infants in many countries are necessary to prevent the irreparable complications of this condition [3]. The risk factors of neonatal hypoglycemia involve maternal diabetes, gestational hypertension, septicemia, and prolonged labor. Other factors include prematurity, perinatal asphyxia, macrosomia, neonatal sepsis, cold stress, and respiratory distress [3-5].

Hypoglycemia is significantly common in infants at risk. The incidence of hypoglycemia in large for gestational age (LGA) neonates is 47%, in small for gestational age (SGA) infants, 52%, in babies born to diabetic mothers, 48%, and in preterm and post-term newborns, 54% [6-8]. According to the various statistics that exist regarding the prevalence of neonatal hypoglycemia and its risk factors, in this study, we intend to investigate the prevalence of neonatal hypoglycemia and its risk factors for the first time using a systematic review and meta-analysis method. Because in some previously published studies, the prevalence of hypoglycemia has been reported as low and in others as high, and accurate and uniform statistics about this disease are not available.

Methods

Study protocol

The present research is a systematic review and meta-analysis which examines the prevalence and factors associated with neonatal hypoglycemia in Iran. This study is based on preferred reporting items for systematic review and meta-analysis (PRISMA) statement [9]. The protocol of this study was registered on the PROSPERO website (CRD42021287656).

Search strategy

All articles relevant to the prevalence and risk factors associated with neonatal hypoglycemia in Iran were retrieved using electronic databases, including PubMed, Scopus, Web of Science, Scientific Information Database (SID), MagIran, and Barakat Knowledge Network System, without time and language restrictions. The keywords and MeSH terms used were "infants", "Iran", "blood glucose", "hypoglycemia", AND "risk factor", combined with the boolean operators "and", AND "or". The search process was updated until September 28, 2021. Additionally, the keywords were queried in the Google Scholar search engine, and the first five pages of results were evaluated. A manual search was also performed on the references of all studies included in the meta-analysis process.

Web of science: Searched topics include prevalence-AND (infant, newborn) and (hypoglycemia) AND address: (Iran) AND (risk factors)

PubMed: Prevalence [title/abstract]) AND (hypoglycemia [title/abstract]) AND (infant, newborn [title/abstract]) AND (risk factors [title/abstract]) AND (Iran [affiliation])

Scopus: Title-abstract-keywords (TITLE-ABS-KEY) (risk factors) AND TITLE-ABS-KEY (hypoglycemia) TITLE-ABS-KEY ("infant, newborn") TITLE-ABS-KEY (prevalence) ANDaffilcountry (Iran)

The inclusion and exclusion criteria

PICO: Population, Iranian infants; intervention, none; comparison, none; outcomes, the prevalence of hypoglycemia and its risk factors in infants. The Inclusion Criteria: The inclusion criteria included those studies that evaluated the prevalence and risk factors associated with neonatal hypoglycemia in Iran and had adequate information for data analysis.

The exclusion criteria

Studies that met the following exclusion criteria were excluded from this review, studies on the prevalence of hypoglycemia in non-neonatal groups; studies on the prevalence of neonatal hypoglycemia symptoms; studies that evaluated the prevalence of neonatal hypoglycemia outside Iran; studies with unavailable full texts; studies that lacked adequate information for data analysis; and the low-quality studies based on the Newcastle Ottawa scale checklist.

Qualitative assessment

After specifying the relevant studies, two independent reviewers qualitatively assessed the studies using the Newcastle Ottawa scale. Score 4 was assumed as the cut-off point of this checklist. If the researchers disagreed over the qualitative evaluation of the studies, a third researcher resolves this inconsistency. The Newcastle Ottawa scale checklist evaluates three subsets, selection of groups (4 questions), comparability of groups (1 question), and exposure or outcome (2 questions). This checklist is a valid instrument and has a long history of reliability.

A star system is used to quantitatively assess the study quality. In this system, a maximum of one star is assigned to the studies of the highest quality. A comparable exception was for which a maximum of two stars can be given. Based on this checklist, the articles are ranked from zero (lowest quality) to 10 (highest quality), and an article with a total score below four is considered low quality and excluded from the study [10, 11]. However, no study with a score below four was found in this meta-analysis.

Data extraction

Two researchers independently extracted data from the articles. Researchers prepared a checklist to extract the required information, including the authors' names, sample size, the number of girls and boys, the publication year, location and type of the study, the prevalence of hypoglycemia in girls and boys prevalence of risk factors of neonatal hypoglycemia.

Statistical analysis

The reviewed studies were combined, considering the sample size and variance of each study. The I^2 index and Q-Cochran test were utilized to evaluate the heterogeneity of the studies. The I^2 index is categorized into three heterogeneity levels, low (less than 25%), moderate (25%-75%), and high (above 75%). The fixed-effects model is more suitable for low heterogeneity, while the random-effects model is used for high heterogeneity. Thus, the random-effects model was selected for this study (I^2=97.2%). Meta-regression was applied to assess the relationship between the prevalence of neonatal hypoglycemia in Iran and the variables of "sample size" and "publication year" of the study. Data were analyzed using STATA software, version 14. The significance level for all tests was considered $P<0.05$.

Results

Search results

First, 215 relevant articles were identified by searching the mentioned databases. After checking the titles of the studies, 75 duplicates were dropped, and the abstracts of the remaining 140 articles were examined. Of these, 126 articles that did not meet the quality evaluation criteria were discarded. Eventually, 14 articles entered the quality evaluation phase, and all showed high quality (Figure 1).

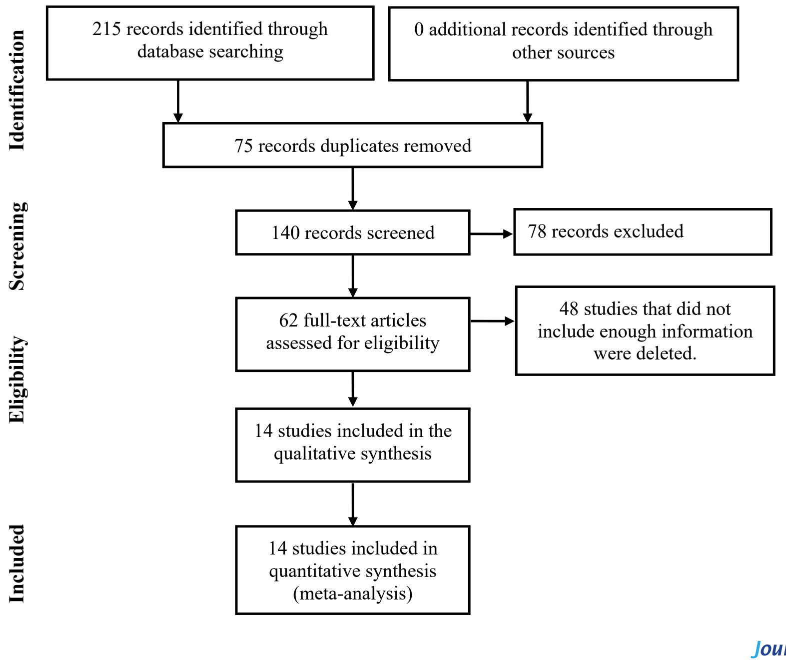

Figure 1. Flowchart of the process of entering studies Into the study of systematic review and meta-analysis

Table 1. The information of the articles entering the systematic review and meta-analysis process

Author, Year of Publication	City of Study	Sample Size	Girls (n)	Boys (n)	Prevalence of Hypoglycemia (%)
Najati & Saboktakin, 2010 [12]	Tabriz	14168	---	---	0.4
Nooripoor et al. 2012 [13]	Semnan	156	---	---	37.2
Hematyar & Mirmajidi Hashjin, 2013 [14]	Tehran	90	50	40	51.1
Akhavan-Karbasi et al. 2002 [15]	Yazd	200	---	---	30.5
Sa'di-nezhad, 2003 [16]	Khorramabad	43	16	27	16.3
Nayeri et al. 2014 [17]	Tehran	219	108	111	11
Sabzehei et al. 2020 [18]	Hamadan	883	442	441	39.1
Mostafa Gharehbaghi & Ghergherehchi, 2016 [19]	Tabriz	100	47	53	33
Kahbazi, 2001 [20]	Arak	284	136	148	52.8
Ghaemi et al. 2009 [21]	Mashhad	927	---	---	11.7
Nasiri et al. 2016 [22]	Sari	204	92	112	21.6
Dashti et al. 2007 [23]	Tehran	673	---	---	15.1
Khalili-Matinzadeh et al. [24]	Tehran	70	26	44	42
Ghafuri, 2005 [25]	Tehran	200	---	---	22.5

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Table 1 provides the specifications of the reviewed articles. The 14 reviewed articles were published from 2001 to 2020 and involved a sample of 18217 newborns. The reported prevalence of neonatal hypoglycemia varied in different regions of Iran and ranged from 0.4% to 52.8%. Overall, the estimated prevalence of neonatal hypoglycemia in Iran was 27% (95% [confidence interval] CI: 18%, 36%) (Figure 2).

A study conducted by Najati et al. [12] was considered irrelevant (due to reporting a close to zero incidence rate for neonatal hypoglycemia) and was omitted from

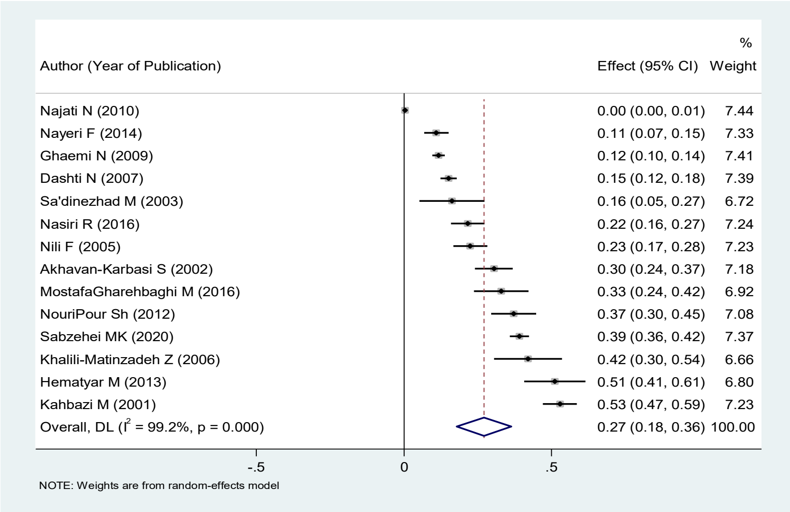

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Figure 2. The prevalence of neonatal hypoglycemia in Iran and its 95% confidence interval from the 14 reviewed studies

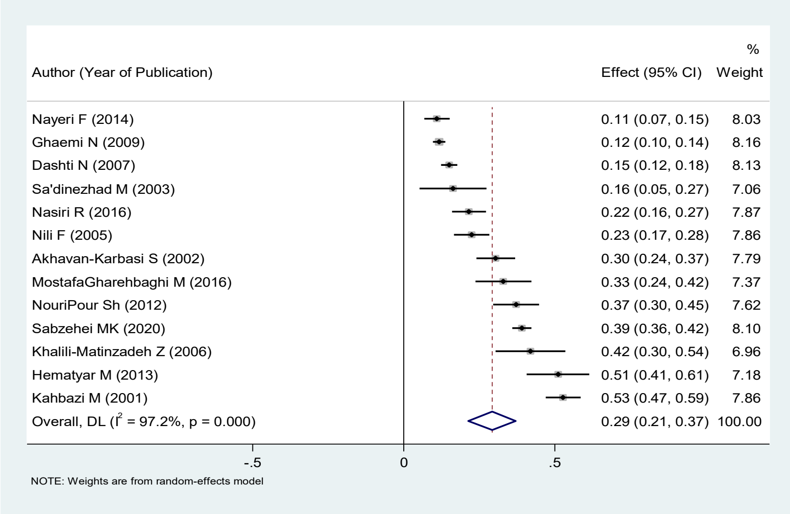

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Figure 3. The prevalence of neonatal hypoglycemia in Iran and its 95% confidence interval from the 13 reviewed studies (after eliminating Najati et al.'s study)

the analysis. Thus, the overall prevalence of neonatal hypoglycemia was reported to be 29% [95% CI: 21%, 37%] for the remaining 13 studies (Figure 3).

Table 2 presents the prevalence and risk factors for neonatal hypoglycemia among the studied subgroups.

As shown in Figure 4, the meta-regression analysis revealed the reduced prevalence of neonatal hypoglycemia in Iran by increasing the sample size of the studies. However, this reduction was not statistically significant (P=0.375).

From Figure 5, the meta-regression indicated that the prevalence of neonatal hypoglycemia in Iran showed an almost steady trend from 2001 to 2020. However, this relationship was not statistically significant (P=0.971).

Discussion

In this meta-analysis, the prevalence of neonatal hypoglycemia was estimated to be 29% [95% CI: 21%, 37%]. Our findings indicated a significant predominance of men in the prevalence of neonatal hypoglycemia. Additionally, the neonatal hypoglycemia prevalence was significantly higher in neonates born via cesarean section delivery than in neonates delivered vaginally. Similarly, many previous studies have stated that cesarean section delivery and anesthesia in mothers raise the risk of neonatal hypoglycemia in healthy and term infants [27], which is consistent with the result of the current meta-analysis.

Concerning the associated risk factors, the lowest and highest prevalence was associated with perinatal asphyxia (8%) and prematurity (61%) in newborns, respectively. Further analysis with meta-regression did not find a statistically significant association between the prevalence of neonatal hypoglycemia in Iran and the variables of "publication year" and "sample size" of the studies.

In a study conducted by Fantahun et al. on 196 newborns in Ethiopia, the hypoglycemia prevalence was 25%. Furthermore, the risk factors of hypoglycemia were identified as prematurity in 35.7%, SGA in 18.3%, maternal diabetes in 1%, and sepsis in 43.8% [27]. Consistent with the results of Fantahun's study, our meta-analysis also indicated prematurity as the most common risk factor of neonatal hypoglycemia.

In another study conducted in Nigeria by West et al. involving 468 infants, neonatal hypoglycemia prevalence was 15.2%. Moreover, the following risk factors were reported, fever in 7%, jitteriness in 2.8%, lethargy in 2.8%, difficulty in breathing in 45.1%, cyanosis in 5.6%, vomiting in 2.8%, apnea in 1.4%, sepsis in 59.2%, jaundice in 57.7%, prematurity in 43.7%, asphyxia in 8.5% and maternal diabetes in 23.9% [28]. Besides, in West et al.'s study, neonatal hypoglycemia due to prematurity was more common compared to neonatal hypoglycemia due to asphyxia and maternal diabetes, which fully corroborates the results of the current meta-analysis. However, the prevalence of hypoglycemia in West's study was almost half of our study, and the number of

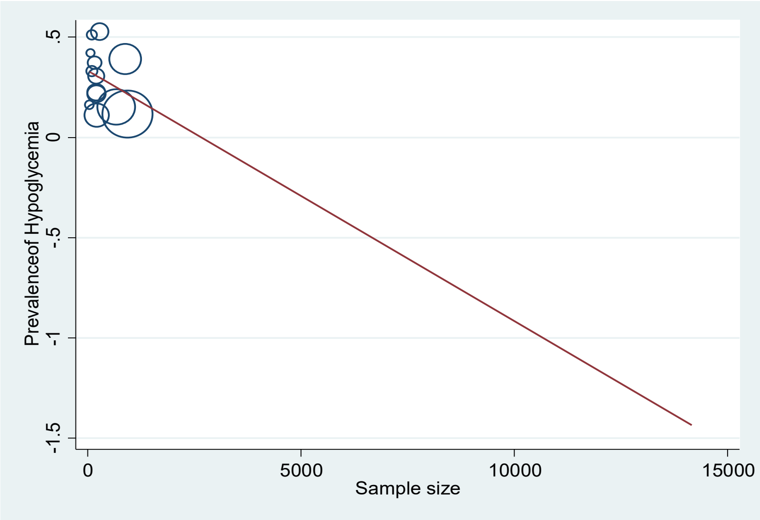

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Figure 4. The meta-regression analysis of the relationship between neonatal hypoglycemia prevalence in Iran and "the sample size of the studies"

newborns and their demographic conditions can be the reason for this difference.

In a study in India in 2021, 150 infants were examined. The researchers in this study showed that premature and post-term, lower (uterine) segment cesarean section (LSCS), LGA, and SGA babies are more prone to developing neonatal hypoglycemia [29]. In a cross-sectional study in Ethiopia, the prevalence of neonatal hypoglycemia was 25%. Also, factors, such as birth weight, duration of delivery, mother's age and time to start feeding, hypothermia, and respiratory distress syndrome were related to hypoglycemia [30]. In a study in the Netherlands, in a cohort study and during 4 years, they examined babies and found that babies with SGA problems are at risk of developing neonatal hypoglycemia [31]. Different factors affect hypoglycemia in babies in different countries.

Conclusion

In 13 reviewed studies, the prevalence of neonatal hypoglycemia was 29% in Iran, meaning that nearly one-third of Iranian newborns suffer from hypogly-

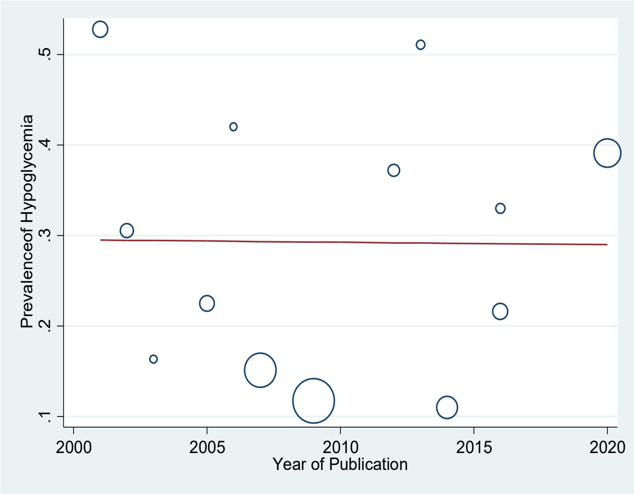

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Figure 5. Meta-regression analysis of the relationship between the prevalence of neonatal hypoglycemia in Iran and "the publication year of the studies"

Table 2. The prevalence and associated risk factors for neonatal hypoglycemia in Iran among the studied subgroups

Variables			%(95 Confidence Interval)
Neonatal hypoglycemia	Total		29(21, 37)
	Sex	Girls	37(23, 51)
		Boys	64(47, 81)
	Type of delivery	Vaginal delivery	24(0, 54)
		Cesarean delivery	67(31, 1.03)
	City	Tehran	27(17, 37)
		Mashhad	12(10, 14)
		Khorramabad	16(5, 27)
		Sari	22(16, 27)
		Yazd	30(24, 37)
		Tabriz	33(24, 42)
		Semnan	37(30, 45)
		Hamadan	39(36, 42)
		Arak	53(47, 59)
Risk factors for neonatal hypoglycemia		Prematurity	61(39, 84)
		Diabetic mother	21(14, 28)
		Septicemia	45(2, 87)
		Perinatal asphyxia	8(5, 12)
		SGA	26(5, 48)
		Hypocalcemia	19(0, 49)
		IUGR	9(7, 12)
		RDS	26(0, 58)
Prevalence of complications for neonatal hypoglycemia		Convulsions	12(2, 21)

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Abbreviations: CI: Confidenc interval; SGA: Small for gestational age; IUGR: Intrauterine growth restriction; RDS: Respiratory distress syndrome.

cemic. Moreover, neonatal hypoglycemia was almost two times more common in male infants compared to female infants. Likewise, the prevalence of neonatal hypoglycemia in infants born to mothers delivered by cesarean section was about 2.5 times that of infants born through vaginal delivery. Hence, this study established the male gender and cesarean section delivery as the risk factors for this condition.

Seizures (12%) were the only complication observed in the present meta-analysis, with one in ten hypoglycemic infants experiencing seizures. The most common risk factors for neonatal hypoglycemia in Iran were infant prematurity, septicemia, prenatal asphyxia, intrauterine growth restriction (IUGR), maternal diabetes, hypocalcemia, SGA, and newborn respiratory distress syndrome (RDS), respectively. Thus, prematurity and perinatal asphyxia were identified as the most common risk factors of neonatal hypoglycemia in Iran.

Limitations

One limitation of the present study was the unavailability of full texts of some articles. Another limitation included the non-uniform distribution of studies because such research has not been performed in some Iranian cities. Furthermore, most articles did not provide basic information, including the age and weight of infants, which precluded us from carrying out a subgroup analysis by infants' age and weight.

Ethical Considerations

Compliance with ethical guidelines

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Funding

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Authors contributions

Conceptualization and design: All authors; Data analyzis: Melina Ramezanpour, Mohammad Yousofpour and Moloud Fakhri; Interpreting the results: Roya Farhadi and Melina Ramezanpour; Revising the manuscript and critically evaluating the intellectual contents: Mahmood Moosazadeh and Moloud Fakhri. Final approval: All authors.

Conflicts of interest

The authors declared no conflict of interest regarding the contents of this article.

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