Glucose-6-phosphate dehydrogenase enzyme deficiency in Iranian newborns: A systematic review and meta-analysis

Review Article

Yadollah Zahed Pasha (MD) [1]
Vahid Zamani (MD) [2]
Ermia Zahed Pasha (MD) [3]
Mohammad Zamani [4, 5 *]

1.Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
ORCID ID orcid.org/0000-0002-3011-0361
2.Vice-Chancellery for Health, Babol University of Medical Sciences, Babol, Iran.
3.Department of Pathology, Rouhani Hospital, Babol University of Medical Sciences, Babol, Iran.
4.Student Research Committee, Babol University of Medical Sciences, Babol, Iran.
ORCID ID orcid.org/0000-0003-1916-3873
5.Cancer Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

* Correspondence:
Mahammad Zamani, Ganjafrooz Street, Babol University of Medical Sciences, Babol, 47176-47745, I.R. Iran.

E-mail: mzamani20@gmail.com
Tel: +98 1132190971
Fax: +98 1132190971

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Abstract

Background: The aim of this study was to perform a systematic review and meta-analysis on available data about glucose-6-phosphate dehydrogenase enzyme deficiency (G6PDD) status in Iranian neonates screened for the disease.

Methods: A literature search was conducted in electronic databases of Embase, PubMed, Web of Sciences, Scopus and Google Scholar for articles published from inception to 1 December 2018. Moreover, the literatures from Iranian databases, including Magiran and Scientific Information Database were searched. We included observational studies reporting prevalence of G6PDD, related complications and genetic factors among Iranian neonates. Data were analyzed using STATA software.

Results: Of 656 articles were initially found, 16 were finally included. Overall pooled prevalence of G6PDD was 5.5% (95% confidence interval: 2-8.9). Analysis also indicated that boys were significantly 3 times more at risk of G6PDD compared with girls. Three articles were identified related to the jaundice and 4 papers related to kernicterus. A range of 43-67% of newborns with G6PDD presents with jaundice. Additionally, 5-9% of G6PDD cases with jaundice present with kernicterus. One article reported that out of 412 newborns, 12.9% were carriers for one of the three G6PD gene mutations, including Mediterranean, Chatham and Cosenza.

Conclusions: Prevalence of G6PDD in Iran is comparable to most countries. Jaundice and kernicterus are major complications of G6PDD. Therefore, it is necessary to pay attention to all patients with G6PDD. Also, it is recommended that hospitals provide the result of G6PD testing as soon as possible and before discharging newborn children.

Keywords: Glucose-6-phosphate dehydrogenase enzyme deficiency, G6PD, Hemolytic anemia, Jaundice, Kernicterus

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Introduction

Glucose-6-phosphate dehydrogenase enzyme deficiency (G6PDD) is an X-linked genetic disease caused by mutations in the G6PD gene, and is the most common enzymopathy in the world [1]. It is reported that this disease worldwide affects approximately 400 million people and 11 million infants with G6PDD, born every year [2, 3]. G6PDD has a prevalence of 5-25% in areas where malaria is endemic, and <5% in non-endemic areas [4]. G6PD enzyme exists in all body cells and has an important role in protecting against oxidative stress. In the patients with G6PDD, due to is oxidation of the red blood cell membrane, the cells are destroyed, causing hemolysis [5].

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Although G6PDD is usually asymptomatic, it can have serious clinical features –that is, hyperbilirubinemia and jaundice, both of which result from an increased rate of hemolysis [6, 7]. One of the important risks of hyperbilirubinemia is kernicterus, which can cause irreversible neurologic complications and permanent developmental disorders observed more frequently in neonates [8, 9]. Because the complications of G6PDD are more serious in newborns, it is necessary to determine the presence of this genetic disease early in this age group.

Health care systems around the world consider a screening program as an important and efficient step in the reduction of hospitalization caused by favism (a form of hemolytic anemia caused by contact with broad beans) and also kernicterus. Most of countries have this program in neonates [10, 11]. In Iran, there is a newborn screening program for G6PDD and it is managed by the Ministry of Health and Medical Education [12]. We aimed to perform a systematic review and meta-analysis on the available data about G6PDD prevalence in Iranian neonates screened for the disease. In addition, it was tried to collect the information related to the genetic factors associated with G6PDD and complications which occur following the disease. These data should be useful for clinicians and other health professionals planning for better management of G6PDD in Iranian newborns.

Methods

Information sources and search strategy: A literature search was conducted in the electronic databases of Embase, PubMed, Web of Sciences, Scopus and Google Scholar for articles published from inception to 1 December 2018. After searching the related terms in the Medical Subject Headings (MeSH) database, finally, the keywords included “glucose-6-phosphate dehydrogenase deficiency” OR “Glucosephosphate Dehydrogenase Deficiency” OR “Glucose 6 Phosphate Dehydrogenase Deficiency” OR “G6PD deficiency” AND “Iran” OR “Iranian”. The search was limited to Title/Abstract. The word “Iran” was limited to Affiliation as well. Furthermore, the current study searched literatures from Iranian databases, including Magiran and Scientific Information Database (SID), using the Persian equivalent of the above-mentioned keywords. Hand searching was also performed on the reference lists of the relevant review articles and studies finally included in the current study to identify additional sources.

This systematic review and meta-analysis were conducted according to the guideline of Preferred reporting items for systematic review and meta-analysis (PRISMA) [13]. The protocol of the present study is available in the PROSPERO registry, too (CRD42019119693) [14].

Inclusion and exclusion criteria: We included observational studies reporting the prevalence of G6PDD among Iranian neonates. To have an acceptable and real prevalence, we included the studies screening for G6PDD in newborns, but we excluded from further analyses conducted only on the subjects with jaundice/hyperbilirubinemia or any other specific disease. We included the later studies for assessment of complications of G6PDD and genetic factors potentially associated with the disease. The other exclusion criteria were the following:

1. Reviews, case reports, editorials, letters and comments,
2. Duplicate articles,
3. Studies conducted on subjects other than neonates,
4. Articles without clear methodology or results, and Full-texts were not available.

Study selection and data extraction: Two authors (MZ, VZ) assessed the Titles and Abstracts independently for eligibility. Besides, the full-text of the potential articles was evaluated in the next step. When there was a discrepancy, it was resolved by consensus with a third author (YZ). Two authors (MZ, EZ) extracted data independently. The following data were collected: first author's name, study period, publication date, study location, number of population (total and by gender), prevalence of G6PDD among screened neonates, prevalence of complications in newborns with G6PDD. Duplicate articles were excluded and one with more details or larger sample size was selected.

Quality assessment: The checklist by Hoy et al. [15] was used for evaluating the risk of bias, which has nine questions with two potential responses (Yes/No). The range of scores is between 0 and 9. Higher scores are representative of higher risk of bias.

Study outcomes and statistical analysis: After collecting the necessary data, they were analyzed using STATA software (StataCorp, College Station, TX, USA). The pooled estimate rate of G6PDD prevalence was presented as percent and 95% confidence interval (CI). The complications of G6PDD in the present study were jaundice (in neonates with G6PDD) and kernicterus (in G6PDD cases presented

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with jaundice). Additionally, the sub-group analyses were performed by gender (male and female) and study date (<2007 and ≥2007). Splitting the study date into <2007 and ≥2007 was mainly based on the distribution of the number of reports in each period category. When the study date was not mentioned, the year of study publication was used instead. Prevalence of G6PDD was compared according to gender by using an odds ratio (OR) with a 95% confidence interval (CI). I2 statistic and χ^2 test were used for checking the statistical heterogeneity. Random effects model was used for meta-analysis. Forest plots were provided to summarize the results of meta-analyses.

Results

A total of 656 articles were initially found by searching the databases, of which 198 papers were excluded after evaluating title/abstract. After assessing full-texts of 35 articles, 19 studies were excluded. Different steps of systematic review were indicated in PRISMA chart (Figure 1). Overall, 16 studies were included in the systematic review for final analysis and their details were summarized in table 1.

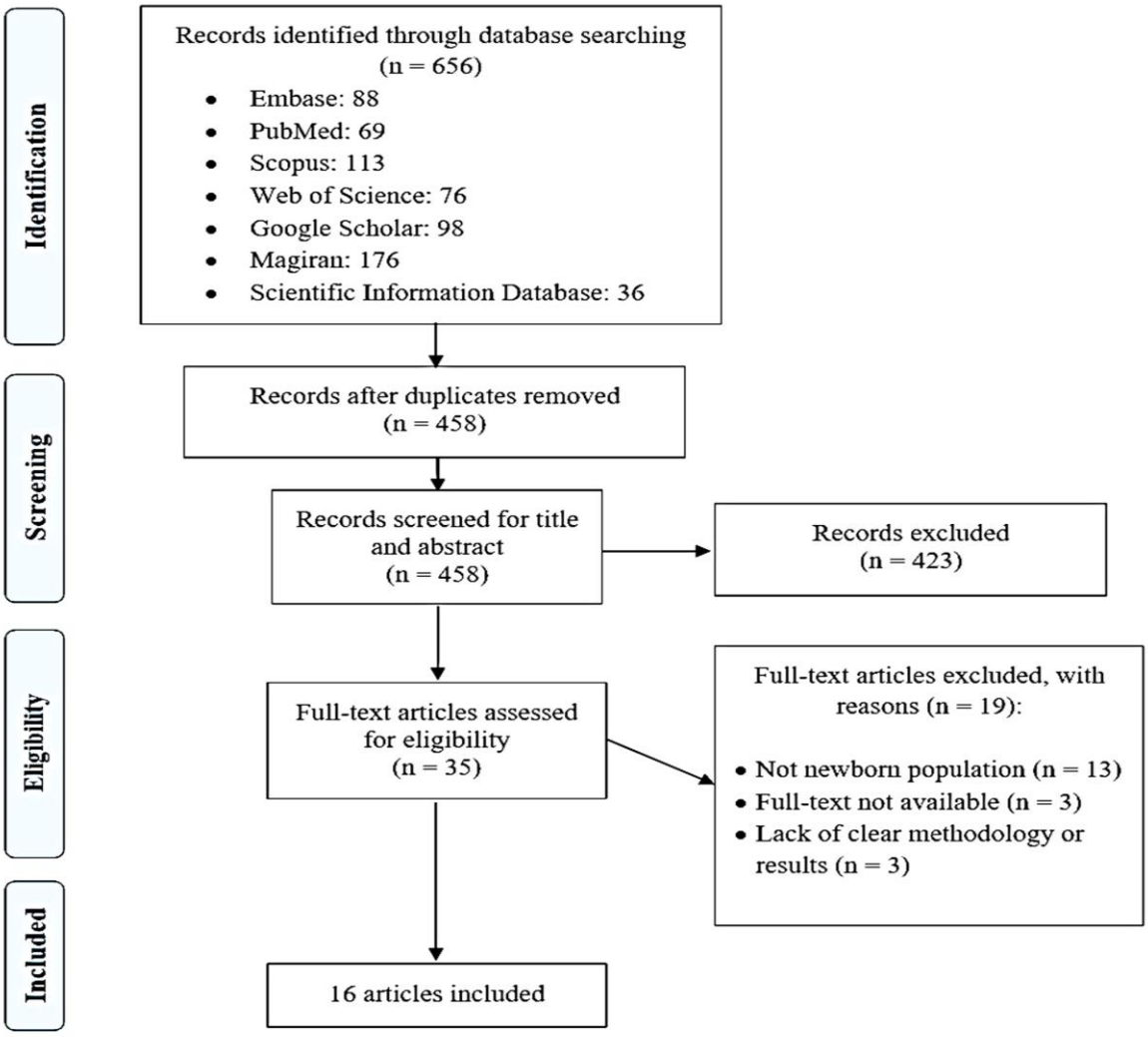

Figure 1. Prisma Flowchart

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Table 1. Charactritics of the studies reproting prevalence of G6PDD among Iraninan newborns screened for the disease

Region	Author	Publication date	Study date	Risk of bias score	Number (total)	Number (boys)	Number (girls)	Prevalence (%, total)	Prevalence (%, boys)	Prevalence (%, girls)
Babol	Zahedpasha (54)	1999	1995	1/9	2046	1035	1011	8.3	12.5	4.1
Bushehr	Movahhed (55)	2003	1998	1/9	415	218	210	8.4	12.8	1.9
Fars	Daliri (56)	2017	2011-2015	1/9	383463	199536	183927	15.6	16.3	14.9
Isfahahn	Iranpour (57)	2008	2006	1/9	2501	1307	1194	3.2	5.1	1
Mashhad	Mohammadzadeh (58)	2009	2006	1/9	2570	1307	1263	0.8	1	0.5
Mazandaran	Kosaryan (59)	2011	2007-2010	1/9	115622	59430	56192	5.8	-	-
Rafsanjan	Alidalaki (60)	2007	2004	1/9	1018	523	495	5	5.7	4.2
Rasht	Khalili (61)	2007	2001	1/9	1197	605	585	6.4	9.8	3.1
Rasht	Keihanian (62)	2016	-	1/9	1474	757	717	6.6	11.4	1.7
Sari	Kosaryan (63)	2014	2012-2013	1/9	365	174	191	7.5	7.5	0
Semnan	Nazari (64)	2011	2007-2010	1/9	9353	4820	4533	3.2	5.5	0.8
Shahrekord	Norbahksh (65)	2013	2011	1/9	1240	633	607	2.3	2	2.6
Sistan and Baluchestan	Ansari-Moghaddam (66)	2017	-	1/9	140	68	72	8.4	11.8	5.6
Tehran	Abolghasemi (17)	2004	1999	1/9	2000	1006	994	2.1	3.6	0.6
Tehran	Khalesy (16)	2012	2008-2009	1/9	450	245	205	2	3.3	0.5
Tehran	Kazemi (18)	2013	2009	1/9	1226	585	641	2.2	2.1	2.3

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Table 2. Rate of jaundice in neonates with glucose 6-phosphate dehydrogenase deficiency and kernicterus in those presented with jaundice in Iran

Complication	Author	Number of subjects	Prevalence of complication (%)
Jaundice	Abolghasemi (17)	42	42.9
	Kazemi (18)	27	70.3
	Khalesy (16)	9	66.7
Kernicterus	Aletayeb (19)	112	4.5
	Boskabadi (20)	59	6.8
	Boskabadi (22)	45	8.9
	Yousefi (21)	34	8.8

Prevalence:

Analysis of 16 articles showed that the overall prevalence of G6PDD in Iran was 5.5% (95% CI: 2-8.9) (Figure 2). The highest rate was for Fars (15.6%) and the lowest one pertained to Mashhad, Razavi Khorasan (0.8%). In addition, the overall pooled prevalence of G6PDD was 7.3% (95% CI: 2.8-11.8) in boys and 3.1% (95% CI: 0-7.6) in girls (Figure 3). Subgroup analysis by study date indicated that the overall estimated prevalence of G6PDD was 4.8% (95% CI: 2.8-6.7) based on studies conducted before 2007, and 5.9% (95% CI: 1.4-10.5) based on studies performed after 2007 (Figure 4). Analysis also suggested that boys were significantly 3 times more at risk of G6PDD than girls (OR=3.1, 95% CI: 1.8-5.3) (Figure 5).

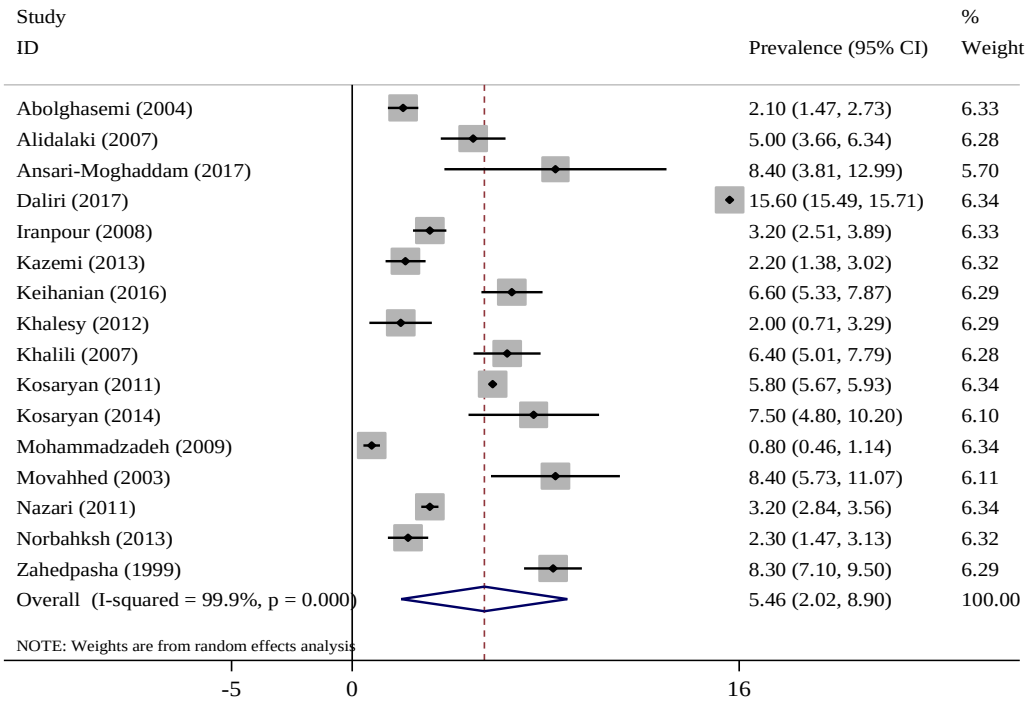

Figure 2. The overall pooled prevalence of G6PDD in Iranian newborns

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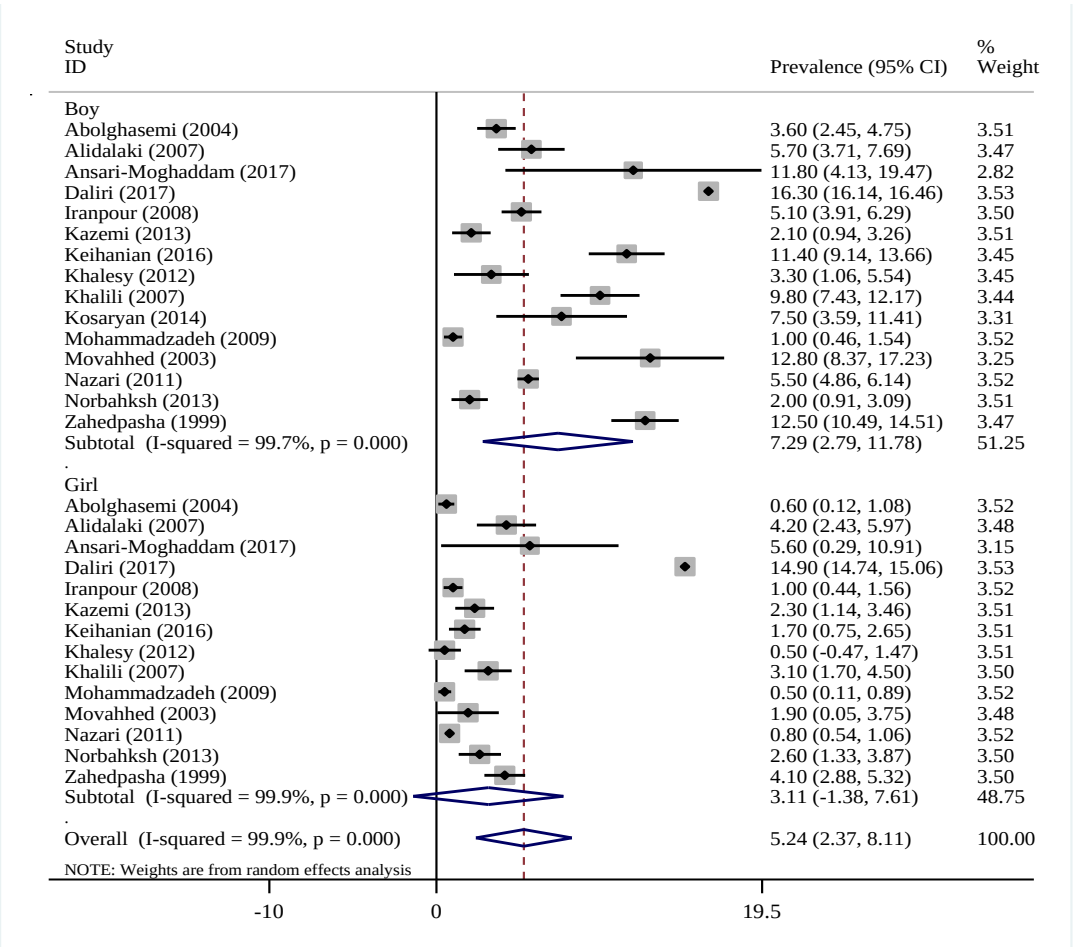

Figure 3. The overall pooled prevalence of G6PDD in Iraninan newborns by gender

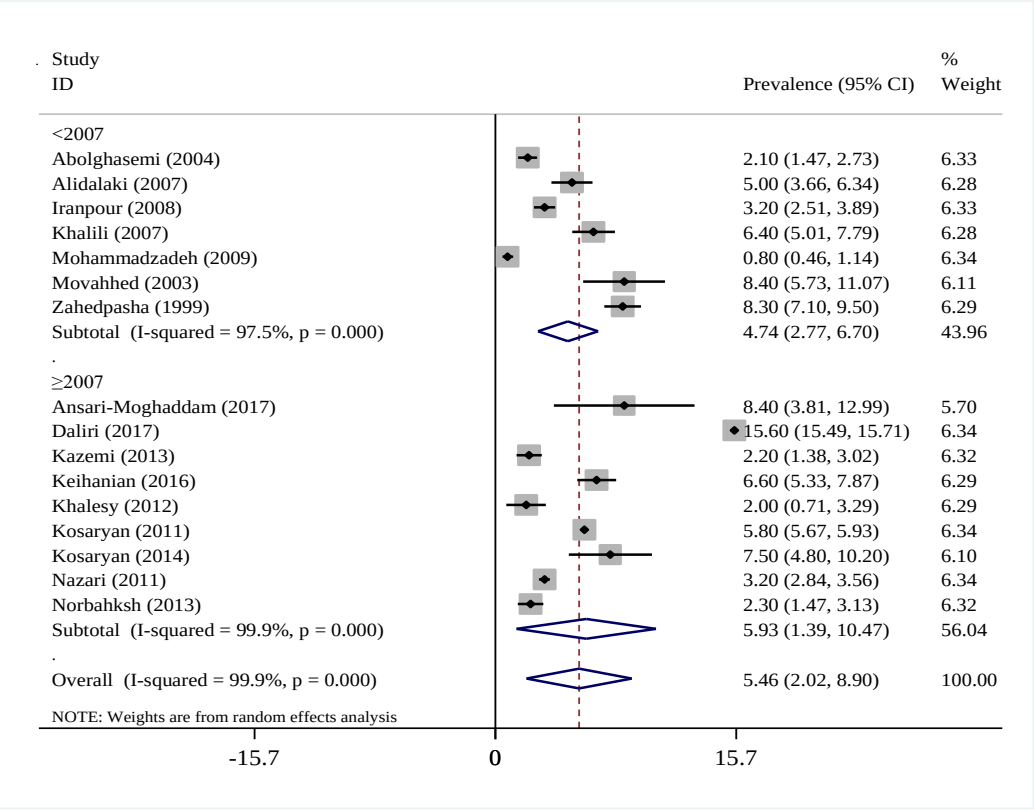

Figure 4. The overall pooled prevalence of G6PDD in Iraninan newborns by study date

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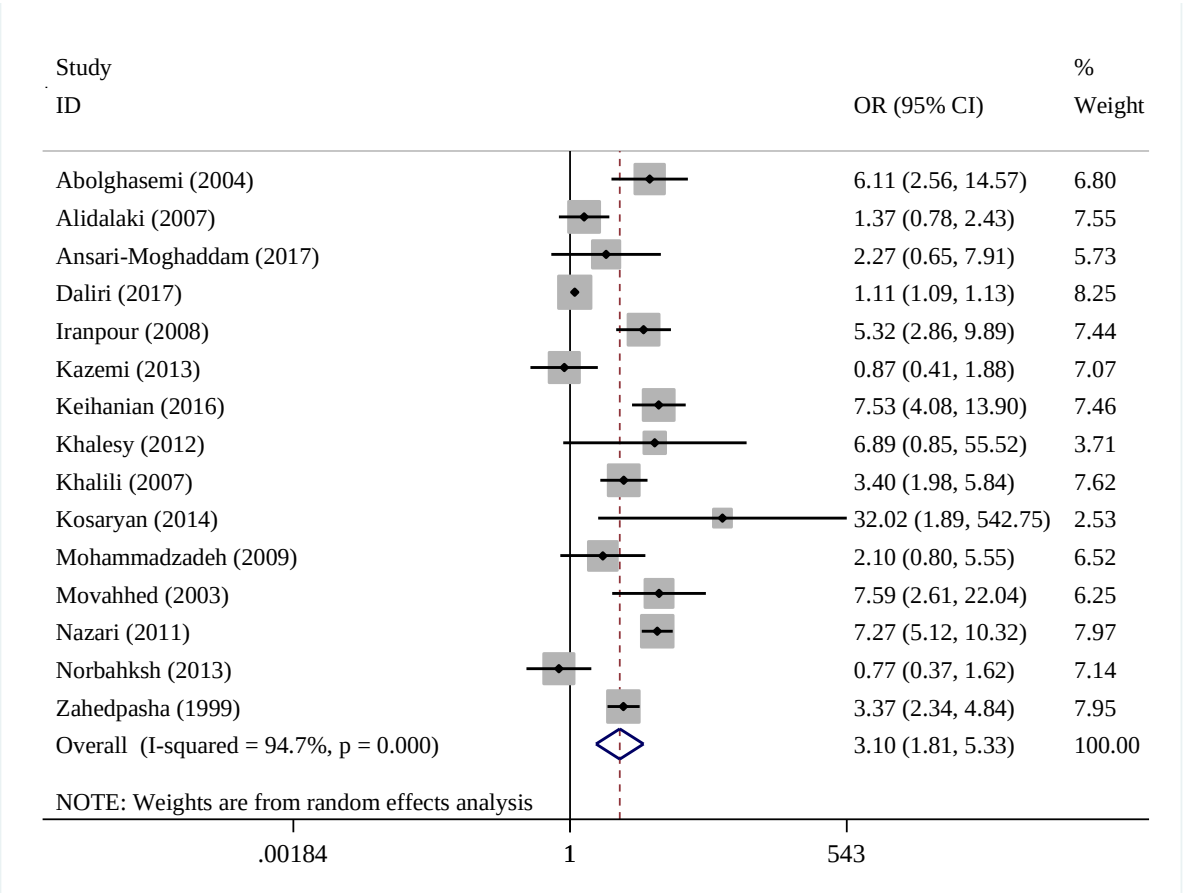

Figure 5. Pooled Odds Ratio (OR) for G6PDD in boys compared with girls

Complications:

In the present systematic review, also it was tried to find the data on the complications of G6PDD among Iranian newborns, including jaundice and kernicterus. After searching the databases, 3 articles [16-18] were identified related to the jaundice and 4 papers [19-22] related to the kernicterus (Table 2). Based on the reports, it was determined that a range of 43-67% of newborns with G6PDD presented with jaundice. In addition, 5-9% of G6PDD cases with jaundice presented with kernicterus, too.

Genetic factors:

Limited number of articles was found that reported genetic factors in G6PDD Iranian newborns. There was only one article assessing the frequency of G6PD mutations, which was carried out in the North of Iran. Mahdavi et al [23]. Stated that 12.9% of 412 newborns (8.6% of boys and 16.8% of girls) were carriers for one of the three G6PD gene mutations including Mediterranean, Chatham and Cosenza. The Mediterranean type was the most frequent mutation among the three examined molecular mutations.

One study by Zahedpasha et al [24]. In Northern Iran investigated the association between the three mutations of G6PD and jaundice. After comparing the distribution of Mediterranean and Chatham mutations between icteric and non-icteric neonates (both with G6PDD), no any significant differences were recognized. On the other hand, the distribution of rare mutations (Cosenza negative) was significantly higher in non-icteric than in icteric newborns. Some mutations of G6PD gene may less likely lead to neonatal icterus, for example, neonates with the rare Chatham mutation are less in need of exchange transfusion,

A different survey by Zahedpasha et al [25]. evaluated any possible relation between neonatal icterus and Gilbert syndrome in newborns with G6PDD, but no any significant differences were found between icteric and non-icteric subjects in the distribution of Gilbert syndrome.

Discussion:

In this systematic review and meta-analysis, it was determined that the prevalence of G6PDD among Iranian newborns was 5.5%. We included the studies in which the newborns underwent screening for G6PDD. There are different studies about G6PDD prevalence in neonates worldwide. For instance, the screening studies on neonates demonstrated G6PDD rates as 11.1% in

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the United States, [26] 4.5% in India, [27] 6.1% in Thailand, [28] 2.4% in China, [29] 7.8% in Brazil, [30] 4.3% in Egypt, [31] 4.4% in Tunisia [32] and 2% in Saudi Arabia [33]. Variable prevalence between different countries and regions can be explained by differences in ethnicity and genetic distribution between populations. Many G6PD gene mutations are responsible for deficiency of the enzyme, including Mediterranean, Chatham, Cosenza, and G6PD A and so on. In a systematic review, only one article was found that reported on the prevalence of G6PD mutations among Iranian newborns [23].

In a recent meta-analysis concerning Iran, the prevalence of Mediterranean, Chatham, and Cosenza molecular mutations was estimated 78.2, 9.1 and 0.5% in G6PD-deficient people, respectively [34]. Mediterranean G6PD has a high prevalence in other tropical and subtropical regions [24]. Its prevalence is similarly high in neighboring countries, such as Saudi Arabia (80%), Oman (74%), Turkey (77%), India (60.4%), United Arab Emirates (55.5%) and Pakistan (76%), as well as in Mediterranean coast countries [34]. This mutation is mainly associated with favism [35, 36]. Chatham mutation is responsible for G6PDD class II presenting with severe hemolytic anemia; however, it has lower prevalence compared with the Mediterranean mutation [37-39].

Our subgroup analysis showed a 3-fold higher rate of G6PDD in boys than in girls and risk of G6PDD, a result that was consistent with previous research [40]. Considering that inheritance G6PDD has an X-linked pattern, it is expected to see this disease more in male infants than in female ones. Homozygous males with class I mutations usually develop chronic non-spherocytic hemolytic anemia, whereas females who are heterozygous for G6PD can carry severe mutations but may remain symptomless [41, 42].

Neonatal screening for G6PDD is implemented in many Asian, African, Mediterranean and Middle Eastern countries where G6PDD is common. Screening is associated with a reduced incidence of severe hyperbilirubinemia and kernicterus. In countries where G6PDD is historically less common, the increase in global population movement has raised the question as to whether G6PDD screening should be implemented throughout the world [31, 41].

There was only one article about the relation between G6PD mutations, jaundice and its treatment in Iranian neonates; Zahedpasha et al [24]. Reported that there were no significant relationships between major mutations and icterus. A recent meta-analysis on five papers represented that infants with G6PDD are about 4 times more at risk of hyperbilirubinemia compared with G6PD-normal infants [42].

The current research also discussed kernicterus - a major complication of G6PDD. It is clear that G6PDD contributes to kernicterus via at least 2 mechanisms: firstly, severe hemolysis results in rising total bilirubin levels and subsequent accumulation of bilirubin in the brain. Secondly, G6PDD results in a reduced buffering capacity against bilirubin-induced reactive oxygen species [43, 44]. The second mechanism may explain why G6PD-deficient infants develop kernicterus at even at lower levels of total bilirubin. The risk of kernicterus in G6PD-deficient infants with total bilirubin serum levels above 20 mg/dL (342 µmol/L) appears to be more severe than that associated with rhesus disease. Thus, in the presence of G6PDD, even more aggressive treatment of these infants is probably indicated [45-48]. The incidence of kernicterus in Iran has risen in recent years because of a variety of factors: firstly, newborns are often discharged from the hospital within 24 to 48 hours of birth, but total bilirubin levels often peak 4 to 5 days after birth. Secondly, the lack of proper monitoring at home allows the undiagnosed development of kernicterus [49-52].

One limitation of this systematic review was the restricted number of studies evaluating complications of G6PDD. The current study suggests the planning of new screening studies, and follow-up of the G6PDD cases to record the frequency of jaundice and kernicterus. Another limitation was the high heterogeneities between the studies, despite analyzing only the population-based screening studies. However, because the individual articles were epidemiologic surveys, we would expect high heterogeneity [53].

In conclusion, the prevalence of G6PDD in Iran is similar to most countries. Jaundice and kernicterus are the major complications of G6PDD. Therefore, it is necessary to provide good care for patients with G6PDD, and it is recommended for those hospitals to provide the result of G6PD testing as soon as possible after delivery, ideally before discharging newborn children.

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