Systematic Review

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Congenital Hypothyroidism Screening Program in Iran; a Systematic Review and Metaanalysis

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Abstract

Objective: Unrecognized congenital hypothyroidism (CH) leads to mental retardation. Newborn screening and thyroid therapy started within 2 weeks of age can normalize cognitive development. In this systematic review, the local results of the national CH screening program in different provinces in Iran are reviewed and evaluated.

Methods: Literature on the CH screening, the national databases including SID, Medlib, Iran Medex, Magiran as well as international databases including PubMed/Medline, ISI Web of Knowledge and web of science, EMBASE, SCOPUS and Google Scholar. Appraisal was guided by a checklist assessing clarity of aims and research questions. The 95% confidence intervals were calculated by I-square models. Meta regression was introduced to explore the heterogeneity between studies.

Findings: We identified 25 samples including 1425124 neonates in our country. Data were Meta analyzed using random-effects models, and we found a TSH levels of 19633 babies in the first sampling were greater than the cut-off level (TSH ≥5mIU/L). The pooled recall rate was 0.014 (95 % CI: 0.013 – 0.015). According to Meta analysis the overall incidence of CH was 2/1000 (95% CI: .002 – .002). The incidence of CH did not appear to be increasing over time (P=0.08).

Conclusion: Considering TSH ≥5mIU/L as a cut-off point for recalling neonates and low positive predictive value (14%) of this point shows that more investigation and research is needed for establishing accurate level of TSH as a criterion for recalling patients.

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Key Words: Congenital Hypothyroidism; Hypothyroidism; Congenital; Meta Regression; Iran

Introduction

Congenital hypothyroidism (CH) is one of the most important causes of preventable mental retardation. The goal of neonatal CH screening programs is early diagnosis and treatment[1]. The delayed diagnosis made only on the basis of clinical findings may result in irreversible complications such as mental retardation and deafness[2,3]. The difficulty in recognizing CH and the serious consequences of delayed therapy have led to the introduction of screening programs for hypothyroidism in newborns by measuring thyroxine (T4) or thyroid-stimulating hormone (TSH or thyrotropin) in spots of blood collected via heel stick during the first few days of life[4].

Screening programs for CH have been developed in Canada, the United States, parts of

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Mexico, Western Europe, Japan, Australia and New Zealand, and they are under development in parts of many countries in Eastern Europe, Asia, South America and Africa. Of the worldwide birth population of 127 million, it is estimated that 25 percent undergo screening for CH[5]. In Iran the screening program was first carried out in 1987 by Azizi et al[6] and was included to the health care service in 2005. Early diagnosis, made possible by neonatal screening, has increased the need for etiologic classification at a very young age, both for the treatment of the affected neonates and genetic counseling of the family[7].

In Iran, preliminary studies on national CH screening program have emerged [11-35]. Within the above-mentioned background we reviewed the local results of the national CH screening program in different provinces of the country in terms of TSH cut-off level. Frequency of cases that required recall and treatment along with stages of the disease before treatment in boys and girls are evaluated.

Subjects and Methods

We identified publications estimating and reporting of results for national CH screening program among Iranian neonates in September 2013 that were published between January 1, 1995 and August 31, 2013. The review is conducted in accordance with PRISMA guidelines[8]. Literature on the CH screening program among Iranian neonates was acquired through searching the national databases including: Scientific Information Databases (SID), Global Medical Article Limberly (Medlib), Iranian Biomedical Journal (Iran Medex), Iranian Journal Database (Magiran) as well as international databases including PubMed/Medline, ISI Web of Knowledge and web of science, EMBASE, SCOPUS and Google Scholar. The search strategy was limited to the Persian and/or English language and articles published up until August 31, 2013 were considered. All publications with medical subject headings (MeSh) and keywords in title, abstract and text for words including congenital hypothyroidism and Iran were investigated. Iranian scientific databases were searched only using the keyword 'Congenital hypothyroidism', as these databases do not distinguish synonyms from each other and do not allow sensitive search operation using linking terms such as 'AND', 'OR' or 'NOT'. Consequently, this single keyword search was the most practical option. The Congenital hypothyroidism, Hypothyroidism, Congenital and Iran MeSh combined with the operator "OR" vs "AND".

All identified papers were critically appraised independently by two reviewers. Disagreements between reviewers were resolved by consensus. Appraisal was guided by a checklist assessing clarity of aims and research questions. inclusion criteria were all related articles published from the local results of the national CH screening program in Iran (notates between the 3rd and 5th day of life on filter paper, by puncturing the heel) using valid databases. Studies upon neonates overlapping time intervals of sample collection from the same origin (for example articles published in both Persian and English language), inappropriate study design and inadequate reporting of results were important exclusion criteria.

The data were extracted on the year of study, geographical location, gender, author, title, setting of the study, sample size, recall rate and incidence of CH using a standardized and pre-piloted data extraction form. Data extraction was undertaken by the first reviewer and checked by a second reviewer, also the process was discussed and piloted by both reviewers. All identified papers were critically appraised independently by both reviewers. Disagreements were resolved through discussion. Appraisal was guided by a checklist assessing clarity of aims and research questions. These data-abstraction forms were reviewed and eligible papers were entered into the meta-analysis.

I-squared model was used for combining results of studies in meta-analysis[9]. Significance level was <0.1 and I-squared statistic for estimates of inconsistency within the meta-analyses[10].

Univariate and multivariate Meta regression analyses were used to explore possible sources of heterogeneity among studies. We analyzed sources of heterogeneity by subgroup and meta regression analysis using dichotomous and continuous variables. Meta-regression was used to show trend of variation of prevalence during time.

Egger's test was conducted to examine potential publication bias. Egger's test can reveal a symmetric or asymmetric funnel plot. The latter indicates the existence of a significant publication bias or a systematic heterogeneity between studies. Data manipulation and statistical analyses were done using STATA software, version 11.2. *P* values <0.05 were considered as statistically significant.

Findings

The final data-set consisted of 68 publications, 33 studies were excluded as they did not meet the inclusion criteria. There were 7 studies in English and 18 studies in Persian of the finally adopted 25 studies and were published between 1995 and 2013. The studies were conducted in 18 different provinces; these publications provided data on 1.425.124 neonates (Table 1 and Fig 1). TSH levels of 19.633 babies in the first sampling were greater than the cut-off level (TSH ≥5mIU/L). The pooled recall rate was 0.014 (95% CI: 0.013– 0.015) (TSH levels of patients whose first heel TSH level was >5 mIU/L are given in Table 1). According to Meta analysis the overall incidence of CH was 2/1000 live births (95% CI: .002 –.002) (Fig 2). According to subgroup analysis based on provinces the highest incidence occurring in the Markazi province was 0.003 (95%CI: 0.002-0.004) and lowest incidence occurring in Tehran, Gilan, Fars, Kerman, Mazandaran and Zanjan provinces was 0.001 (95%CI: 0.001-0.001) (Table 2).

There were 0.46 (95% CI: 0.45–0.46) female and 0.54 (95% CI: 0.54–0.54) male infants who had CH. In this study there was no statistically significant difference between males and females (*P*=0.5). The heterogeneity between studies was 98.7% with an I-square (I^2) statistics (541.33, DF=7, *P*<0.001).

Fig. 3 shows that the CH incidence has had no increasing trend during 1995 till 2013. Meta-regression analysis found that sample size does

Table 1: Characteristics of included reports

Study location (Province)	Authors	Year of study	No. of patients	Recall rate	Incidence
Khuzestan	Aminzadeh et al[11]	2010	35655	0.0352	0.0020
Tehran	Ordoukhani et al[12]	2002	35067	0.0106	0.0010
Khorasan	Namakin et al[13]	2012	38987	0.0321	0.0183
Gilan	Kalantari et al[14]	2004	3000	0.0200	0.0010
Markazi	Dorreh et al[15]	2010	25658	0.0236	0.0030
Fars	Karamizadeh et al[16]	2012	63031	0.0200	0.0010
Isfahan	Hashemipour et al[17]	2007	113282	0.0320	0.0030
Kerman	Eftekhari et al[18]	2008	3000	0.0070	0.0010
Kurdistan	Nele et al[19]	2011	50539	0.0200	0.0020
Mazandaran	Akhi et al[20]	2011	45218	0.0460	0.0016
Ghazvin	Saffari et al[21]	2009	33488	0.0320	0.0020
Gilan	Mohtasham et al[22]	2007	9284	0.0315	0.0017
Yazd	Nouri Shadkam et al[23]	2008	13022	0.0620	0.0030
East Azerbaijan	Zeinalzadeh et al[24]	2011	62459	0.0250	0.0017
Kermanshah	Khassi et al[25]	2011	30265	0.0018	0.0017
West Azerbaijan	Eshratkhah et al[26]	2011	19141	0.0200	0.0020
Tehran	Mostafavi et al[27]	1995	1014	0.0800	0.0060
Tehran	Ordookhani et al[28]	2003	20107	0.0013	0.0010
Zanjan	Valizadeh et al[29]	2011	18008	0.0410	0.0010
Isfahan	Honarpisheh et al[30]	2002	500	0.0500	0.0100
Isfahan	Hashemipour et al[31]	2010	225224	0.0170	0.0020
Isfahan	Hashemipour et al[32]	2007	93381	0.0111	0.0030
Mazandaran	Haghshenas et al[33]	2012	10573	0.0200	0.0005
Isfahan	Ghasemi et al[34]	2013	464648	0.0210	0.0013
Mazandaran	Nasehi et al[35]	2010	10573	0.0140	0.0140

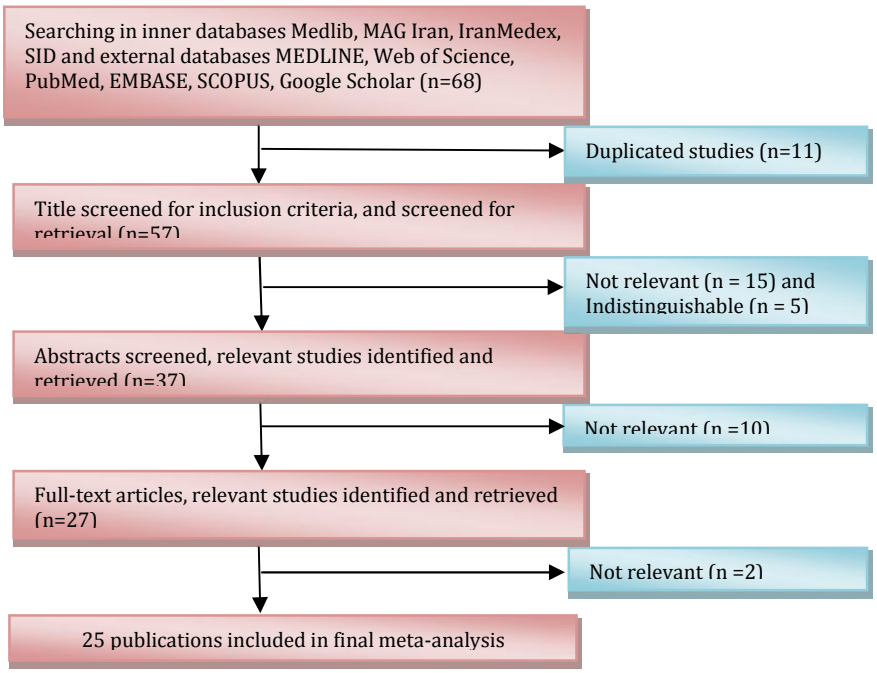

Fig. 1: Flow diagram showing the different steps involved in searching for relevant publications (1995–2013).

not significantly affect heterogeneity for the factor 'CH incidence' (Reg Coef = 0.028, *P*=0.4). Meta-regression showed an association between the year of study and prevalence rate of CH incidence and demonstrated causes of the variability in the results of studies. Meta-regression showed that variability in CH incidence is not a significant effect for years (Reg Coef=0.031, *P*=0.08). There was no evidence of publication bias (Egger's test β0: 0.26; *P*=0.6) (Fig. 4) so we tried to consider

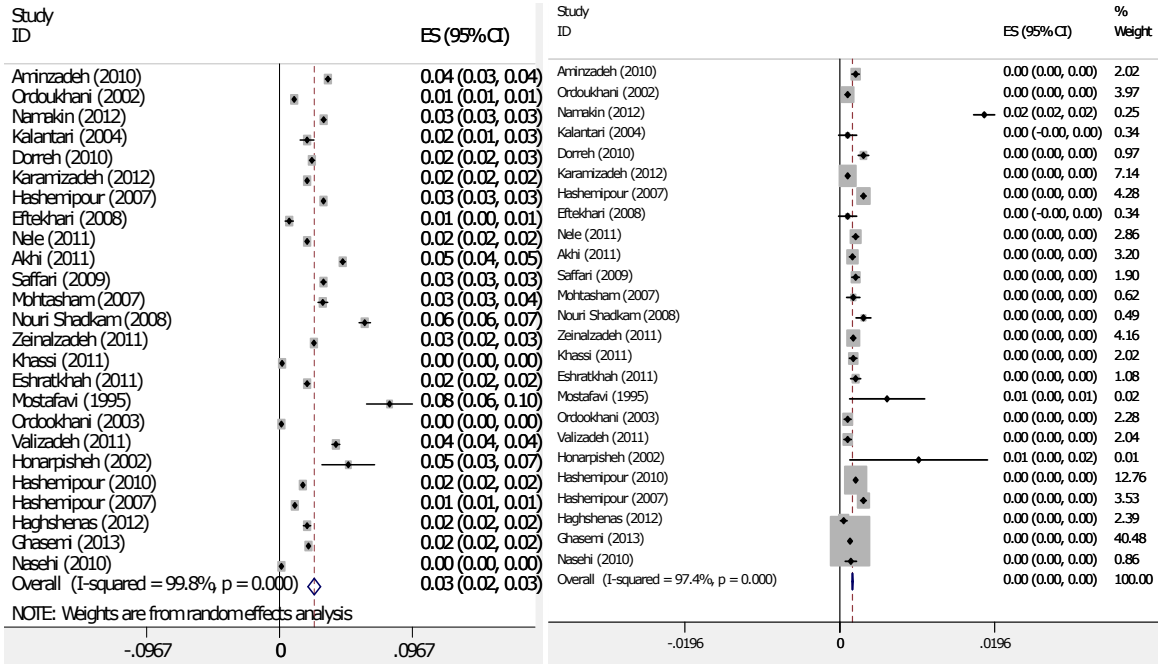

Fig. 2: Forest plots of recall rate (A) and incidence of CH (B) for I-squared model meta-analyses (Weights are from I-squared model). The diamond represents the overall result

Table 2: Subgroup analysis of CH Incidence based on various provinces in Iran

Province	No. of studies	No. of Subjects	CH Incidence (95% CI)	heterogeneity		model
				I-squared	P value	
Khuzestan	1	35655	0.002(0.002-0.002)	0.00	0	I-squared
Tehran	3	56188	0.001(0.001-0.001)	4.24	0.12	I-squared
Khorasan	1	38987	0.018(0.017-0.020)	0.00	0	I-squared
Gilan	2	12284	0.001(0.001-0.002)	0.95	0.33	I-squared
Markazi	1	25658	0.003(0.002-0.004)	0.00	0	I-squared
Fars	1	63031	0.001(0.001-0.001)	0.00	0	I-squared
Isfshan	5	464648	0.002(0.002-0.002)	186.99	0.000	I-squared
Kerman	1	3000	0.001(0.001-0.002)	0.00	0	I-squared
Kurdisatan	1	50539	0.002(0.002-0.002)	0.00	0	I-squared
Mazandaran	3	66364	0.001(0.001-0.001)	15.13	0.001	I-squared
Ghazvin	1	33488	0.002(0.002-0.002)	0.00	0	I-squared
Yazd	1	13022	0.002(0.003-0.004)	0.00	0	I-squared
East Azerbaijan	1	62459	0.002(0.001-0.002)	0.00	0	I-squared
Kermanshah	1	30265	0.002(0.001-0.002)	0.00	0	I-squared
West Azerbaijan	1	19141	0.002(0.001-0.003)	0.00	0	I-squared
Zanjan	1	18008	0.001(0.001-0.001)	0.00	0	I-squared
Pooled of CH	25	1425124	0.002(0.002-0.002)	911.79	0.000	I-squared

most of published articles in this subject.

Discussion

We report a systematic review of the CH screening program in neonates based on 25 separate samples (from 68 publications) based on 1.425.124 neonates. In addition, we have, to our knowledge for the first time, reviewed reports in CH screening program in Iran and employed meta-regression analysis to explore sources of heterogeneity between studies.

The CH screening program has been implemented in Iran since 2006. It is based on TSH measurement by heel prick between the 3rd and 5th day of life. The most important goals of CH screening programs are early diagnosis and treatment of CH. Preferably, the diagnosis must be confirmed within the first 14 days, and treatment must be started. There are also some studies emphasizing the necessity of starting the treatment no later than three months (ideally 1 month) after the first sample[36].

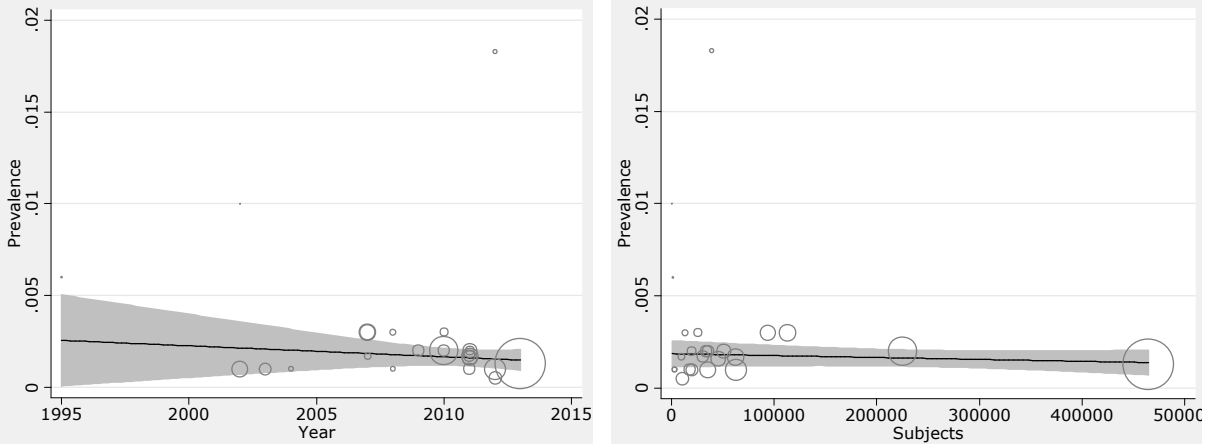

Fig. 3: Meta-regression plots of change in CH incidence according to changes in continuous study moderator's year and sample size

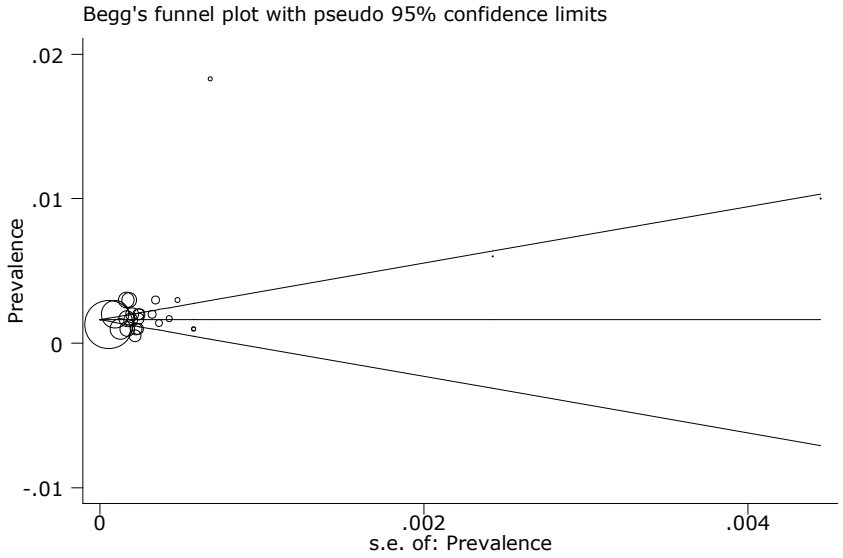

Fig. 4: Begg's funnel plot (pseudo 95% confidence limits) showing means difference in prevalence of hypothyroidism (CH) by standard error of mean difference

The pooled recall rate was (0.014 per case) according to cutoff point for recalling the patients in screening program and the overall incidence of CH was (2/1000 live births). It was reported that the prevalence of CH in the Greek Cypriot population 1990-2000 was 1/1800[37]. The results of the screening program for CH in Italy noted the incidence of CH as 1/1446 between 1999 and 2005[38]. Nonetheless, CH is more common in Eastern countries, for example, the incidence of permanent CH was found as 1/748 in Iran 2002-2005[7]. CH incidence before the CH screening program in Turkey was reported as 1/2736-1/2326[39]. A study from Konya noted that the CH incidence 1999-2007 was 1/2183[40]. At the present time, there is a good policy and appropriate methods are available for screening of CH in Iran, but it seems that the cut-off point for TSH ≥5mIU/L in whole blood overestimates the real number of patients.

According to these findings whole blood TSH≥15mIU/L seems to be a more reliable and cost effective cutoff point for recalling patients in screening programs of CH. In Bosnia and Herzegovina, the TSH cutoff value for recall was ≥20mIU/L in whole blood[41], ≥15mIU/L in Mexico[42] and ≥25mIU/L in Thailand[43].

The strengths of this review include the large number of samples and neonates included, and therefore the ability to examine recall and incidence rates. In conclusion, lowering the cut-off level will probably increase the cost of the screening program; however, the number of the missed cases due to high cut-off levels is substantial. Considering TSH ≥5mIU/L as a cut-off point for recalling neonates and low positive predictive value (14%) of this point shows that more investigation and research is needed for establishing accurate level of TSH as a criterion for recalling patients.

Conclusion

Considering TSH ≥5mIU/L as a cut off point for recalling neonates and low positive predictive value (14%) of this point shows that more investigation and research is needed for establishing accurate level of TSH as a criterion for recalling patients.

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Authors' Contribution

Study design and Collection of the data: Y. Veisani and S. Rezaeian

Data analysis: K. Sayehmiri
Preparation of the manuscript: A. Delpisheh and Y. Veisani
All authors approved final version of the paper.

Conflict of Interest: None

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