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Gender and Risk of Congenital Hypothyroidism: A Systematic Review and Meta-Analysis

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Abstract

Background: Although numerous observational studies have investigated the association between gender and risk of congenital hypothyroidism, the role of gender as a risk factor for congenital hypothyroidism remains unknown. This meta-analysis was conducted to summarize the epidemiologic evidence of the effect of gender on the congenital hypothyroidism occurrence, and also to identify the sex ratio for congenital hypothyroidism.

Materials and Methods: A comprehensive literature search of numerous electronic databases including Medline (via PubMed), Scopus, EMBASE, and Science Direct was performed until February 1st, 2017. All studies designed case-control (six studies with 3,254 subjects) and cross-sectional studies (eight studies with 8,258,745 subjects) addressing the association by odds ratio (OR) and 95% confidence interval (95% CI) were included. Moreover, eleven cross-sectional studies were also included providing a sex ratio for congenital hypothyroidism. Pooled Mantel-Haenszel OR (MH OR) with 95% CI was estimated using the random-effects method.

Results

The overall summary results showed that girl gender is associated with an increased risk of congenital hypothyroidism (pooled MH OR=1.46; 95%CI: 1.10, 1.95). The pooled MH OR for case-control studies was 1.69 (95%CI: 1.35, 2.13), whereas the pooled MH OR for cross-sectional studies was 1.26 (95%CI: 1.00, 1.59). In addition, pooled female to male sex ratio of congenital hypothyroidism incidence was 1.35 (95%CI: 0.99, 1.83).

Conclusion: The results of this meta-analysis provide evidence for a higher risk in girl gender for developing congenital hypothyroidism. More epidemiological and clinical studies are needed to explore why girl gender is at increased risk of congenital hypothyroidism compared with boy.

Key Words: Congenital hypothyroidism, Female, Male, Meta-analysis.

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1- INTRODUCTION

Congenital hypothyroidism, as a most common endocrine disease in newborns, classified into permanent and transient congenital hypothyroidism and affects approximately one in 3,000 to 4,000 live births (1). A number of epidemiological and clinical studies have shown that multiple factors may be involved in congenital hypothyroidism occurrence, including race and ethnicity (2), environmental factors (3), characteristics of birth and pregnancy (4), and screening programs (5, 6). One of the most important and fundamental biologic factors is gender variable which the its inequalities has been reported in the health related outcomes (7).

Although numerous observational studies have also investigated the association between gender and risk of congenital hypothyroidism, the role of gender as a risk factor for congenital hypothyroidism remains unknown. There are inconsistent findings about congenital hypothyroidism occurrence risk with regard to gender. Some researchers have found an increased risk of congenital hypothyroidism in girls (3, 8, 9) whereas others have demonstrated that congenital hypothyroidism occurrence is associated with boy gender (10-12) or no variation by gender (4, 13, 14). In addition to the inconsistencies noted above, many other factors including sample size, chance, study design, different prevalence across the populations, and differing statistical methods may be related to differences in the association between gender and congenital hypothyroidism occurrence. A reliable estimate can be achieved using a comprehensive meta-analysis.

We, therefore, performed a systematic review and meta-analysis to summarize the epidemiologic evidence of the effect of gender on the congenital hypothyroidism occurrence, and also to identify the sex ratio for congenital hypothyroidism.

2- MATERIALS AND METHODS

2-1. Search Strategies

A comprehensive literature searches of numerous electronic databases including Medline (via PubMed), Scopus, EMBASE, and Science Direct was performed using the terms "congenital hypothyroidism and gender", "congenital hypothyroidism and sex", and "congenital hypothyroidism prevalence" up until February 1st, 2017. The search was limited to all studies designed case-control and cross-sectional studies in humans with no language restrictions. The reference list of retrieved papers was manually reviewed to identify additional relevant studies.

2-2. Data Extraction and Quality Assessment

Two independent authors (SR and EH) reviewed the retrieved studies and the following information was extracted: (1) name of the first author, (2) publication year and location of study conduction, (3) study design: cross-sectional or case-control study, (4) type of congenital hypothyroidism (permanent, transient, or mixed), (5) total sample size, (6) the numbers of case and control and reported odds ratio (OR) (in case-control studies), (7) the reported prevalence of congenital hypothyroidism (in cross-sectional studies), (8) number of girls and boys, and (9) sex ratio. The kappa statistics (95%) was used to identify the inter-authors reliability. The third author (SK) was considered as arbiter to resolve any disagreements. The STROBE statement was used to assess the quality of studies (15). All of the studies retrieved in the meta-analysis were assessed as high quality.

2-3. Statistical Analysis

The comprehensive meta-analysis software version 2.0 was used for this meta-analysis. There were found only six case-

control studies addressing the association. Five of them reported unadjusted OR of congenital hypothyroidism risk factors for mixed congenital hypothyroidism (3, 4, 16-18), and one reported separately for permanent and transient congenital hypothyroidism (8). Hence, due to the small number of studies on type of congenital hypothyroidism, stratified analyses were not performed. Eight cross-sectional studies were also found with addressing the association (10, 12, 19-24). In addition, eleven cross-sectional studies were included providing a sex ratio for congenital hypothyroidism (25-35). The pooled Mantel-Haenszel OR (MH OR) with 95% confidence interval (95%CI) estimating the association between gender and congenital hypothyroidism was obtained using the random effect model. In addition, pooled sex ratio (female to male) was computed using the random effects meta-analysis.

The heterogeneity of results across studies was checked using Cochran's Q test (with P-value <0.10) and it was quantified by the I^2 statistic. The I^2 statistic greater than 50% was considered as significant heterogeneity across studies. Tau-squared (t^2 or Tau^2) statistic and Egger's linear regression test were used to explore the between-study variance and to investigate publication bias, respectively (36). The PRISMA statement was used as a guide to better-quality reporting of the current review (37).

3- RESULTS

3-1. Description of studies

The characteristics of the studies included in the meta-analysis are shown in **Table.1**. Of 1,607 retrieved studies, six case-control and eight cross-sectional studies involving 3,254 and 8,258,745 subjects were included in the meta-analysis, respectively. **Figure.1** presents the flow diagram of the literature search process.

3-2. Summary result of the association of gender and congenital hypothyroidism risk

The overall summary results of both case-control and cross-sectional studies (**Figure.2**) showed that female gender increased the risk of congenital hypothyroidism (pooled MH OR=1.46; 95%CI: 1.10, 1.95). There was a significant heterogeneity in the overall pooled MH OR among case-control and cross-sectional studies (I^2=68.38%, $P_{heterogeneity}$<0.001).

Summary results of six case-control studies (**Figure.2**) indicated that female gender was a significant risk factor for occurrence of congenital hypothyroidism (pooled MH OR= 1.69; 95%CI: 1.35, 2.13). There was not heterogeneity in the overall pooled MH OR in the case-control studies (I^2=44.44%, $P_{heterogeneity}$=0.109).

Summary results of eight cross-sectional studies (Figure.2), also indicated that female gender was a significant risk factor for occurrence of congenital hypothyroidism (pooled MH OR= 1.26; 95%CI: 1.00, 1.59). There was a significant heterogeneity in the overall pooled MH OR in the cross-sectional studies (I^2=67.7%, $P_{heterogeneity}$=0.003).

We found a pooled female to male sex ratio of congenital hypothyroidism incidence of 1.35 (95%CI: 0.99, 1.83) with a significant heterogeneity among studies (I^2=79.8%, $P_{heterogeneity}$<0.001).

The pooled female to male sex ratio of congenital hypothyroidism incidence by type of congenital hypothyroidism were 1.53 for mixed, 1.44 for permanent, and 0.78 for transient congenital hypothyroidism (**Figure.3**).

3-3. Publication Bias

The publication bias was assessed using the funnel plot as well as Begg's and Egger's tests. No publication bias was

detected by the results of Begg's and Egger's tests for both case-control (P=0.171) and cross-sectional studies (P=0.881) (**Figure.4**).

Table-1: Characteristics of the studies on the effect of gender and congenital hypothyroidism risk included in the meta-analysis

Study	Country	Study design	Cases	Controls	Patients	Total sample size
Abdelmoktader et al., 2013 (3)	Egypt	Case-control	320	320		
Kurinczuk et al., 2002 (16)	Australia	Case-control	126	1260		
Medda et al., 2005 (8)	Italy	Case-control	155	619		
Rezaeian et al., 2013 (4)	Iran	Case-control	277	1036		
Sepandi et al., 2009 (18)	Iran	Case-control	126	401		
Zhou et al., 2015 (17)	China	Case-control	125	375		
Anastasovska et al., 2014 (19)	Macedonia	Cross-sectional			8	9757
Dorreh et al., 2014 (12)	Iran	Cross-sectional			414	127112
Golbahar et al., 2010 (20)	Bahrain	Cross-sectional			6	17806
Gu et al., 2007 (23)	Japan	Cross-sectional			1586	7503772
Kocova et al., 2015 (24)	Macedonia	Cross-sectional			83	215077
Law et al., 1998 (22)	UK	Cross-sectional			103	302741
Mikelsaar et al., 1998 (21)	Estonia	Cross-sectional			7	20021
Zeinalzadeh et al., 2012 (10)	Iran	Cross-sectional			94	62459

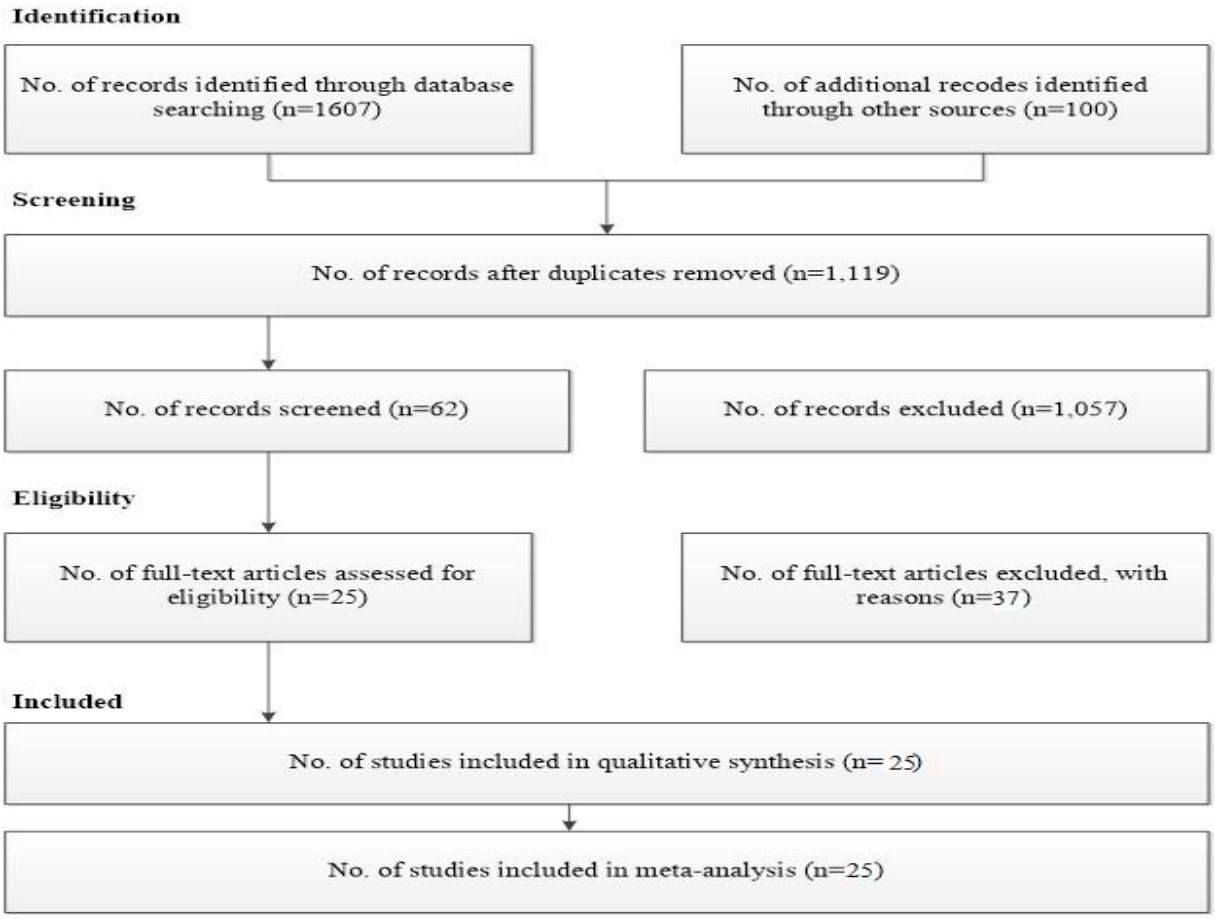

Fig.1: Flow diagram of the meta-analysis.

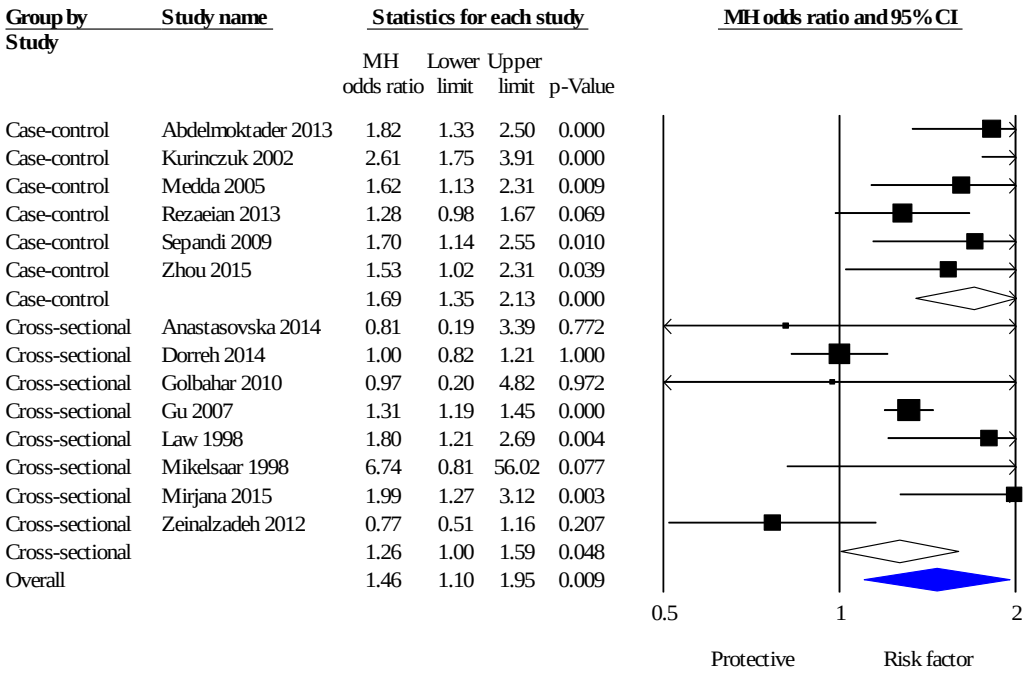

Fig.2: Forest plot of odds ratio estimate of association between gender and congenital hypothyroidism by study type.

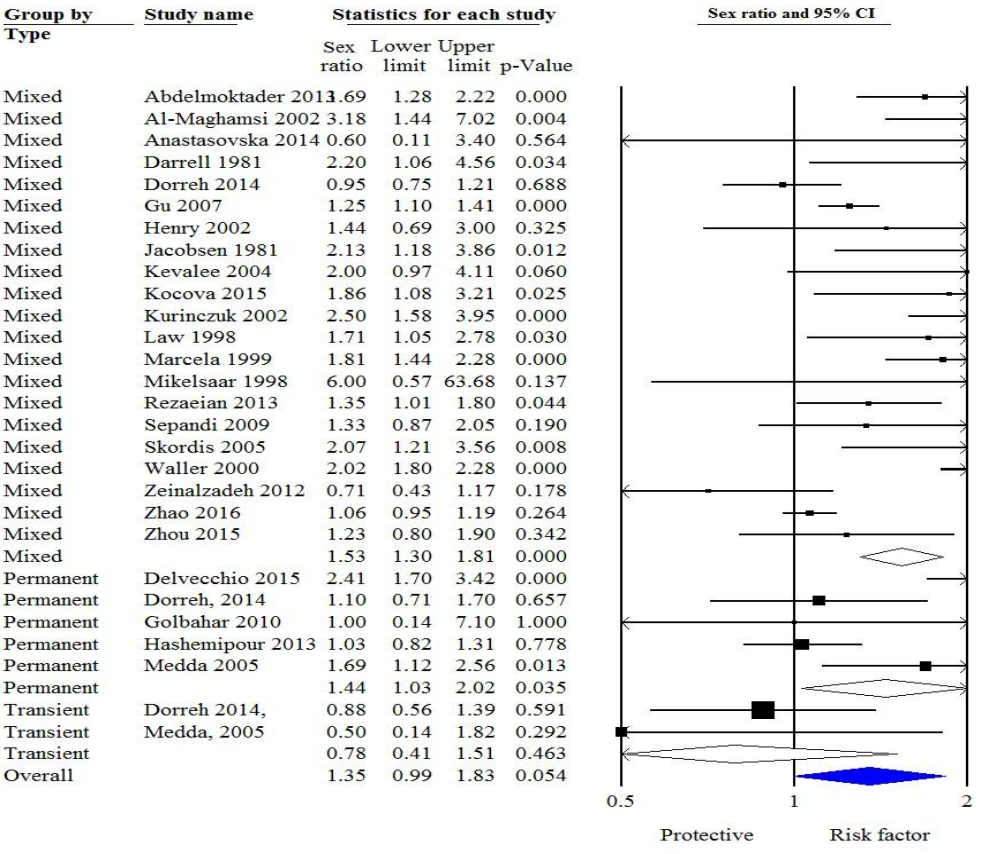

Fig.3: Forest plot of sex ratio for congenital hypothyroidism in total studies by type of congenital hypothyroidism (I^2=79.8, $P_{heterogeneity}$<0.001).

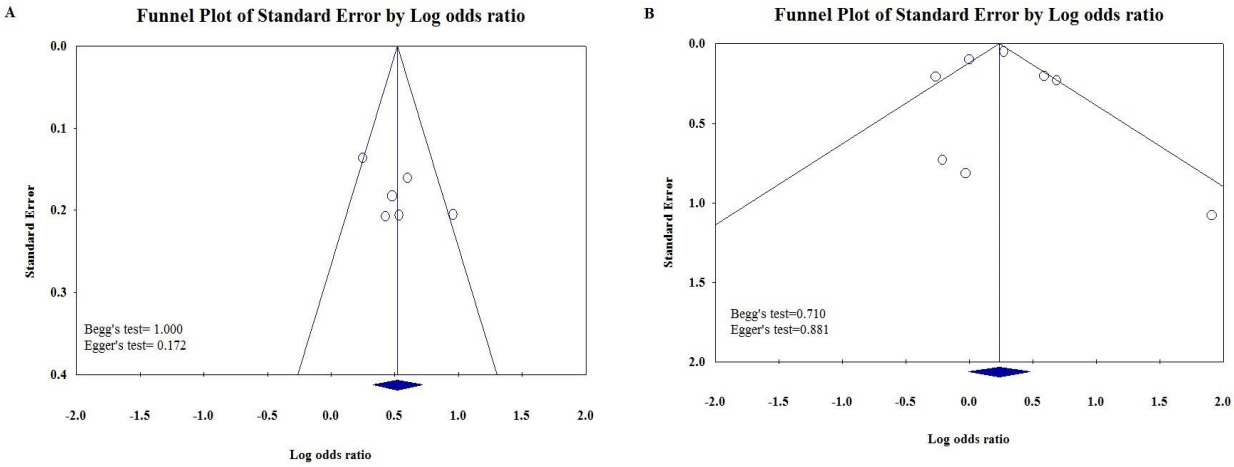

Fig.4: Funnel plot of included studies in the meta-analysis by study design: (A) case-control studies, (B) cross-sectional studies.

4- DISCUSSION

The results of the present meta-analysis suggest a higher chance of developing congenital hypothyroidism in girl infants than boys both in subgroups of case-control and cross-sectional studies. The sex ratio (female to male ratio) of congenital hypothyroidism incidence was also significant which this ratio was 44% higher in girls than boys in permanent type, and 22% was lower in girls than boys in transient type of congenital hypothyroidism. However, the results indicated that female gender is a weak, but significant risk factor to occurrence of congenital hypothyroidism.

Although, a stronger association may be considered as a causal relationship and poor association may be due to confounding factors. However, the weak and significant association does not deny causality connection (38). Given that our results showed contradictory in sex ratio for permanent and transient congenital hypothyroidism, therefore integration of the results may be lead to null in association and subgroup analysis in congenital hypothyroidism types is needed. But due to the small number of retrieved studies based on the type of congenital hypothyroidism the result may not be consistent. Congenital hypothyroidism is considered as a sporadic disease, so that there is no family history in 98% of cases and also in terms of inheritance the rate of disagreement in single-egg twins is 92% (39). In many studies, race (40, 41), environmental factors, (42), and conditions around childbirth (3, 4, 8, 43) has been reported as the major risk factors for congenital hypothyroidism; but there are conflicting results about the role of gender on the occurrence of congenital hypothyroidism (3, 4, 44). A study conducted in the USA (45) on newborn infants during 1993-2000 to investigate the sex ratio of congenital hypothyroidism showed that this ratio in permanent cases always was higher in girls than boys and the ratio was various in different states; but there was no significant difference between two sexes for type of transient (45). Accordingly, difference in sex ratio is related to obtain the same result in population groups with high heterogeneity with regard to race and geographical location. According to this study, the pooled results of 14 studies with a sample size of 8,261,999 subjects in the

different geographical areas of the world with different races could be a significant support for having higher chance of female gender to occurrence of congenital hypothyroidism (45). Although, it is still unclear the reasons for why odds of morbidity in female is higher than boy infants, but the results of a study revealed that the interaction of gender and birth season (summer) increases the likelihood of developing congenital hypothyroidism (46). On the other hand, the gender differences in transient congenital hypothyroidism with boy infants at a higher risk may have been masked by some reasons. There was evidence of heterogeneity and also the sample size was small by subgroup analysis.

4-1. Limitations of the study

There was a potential limitation in this meta-analysis. The included studies have not reported their results by type of congenital hypothyroidism (permanent or transient). We, therefore, could not conduct subgroup analysis based on the type of congenital hypothyroidism. Another limitation regarding search of grey literature is not only for our study but also for the most of the meta-analyses. Despite its limitation, this meta-analysis is the first to explore strong evidence about the effect of gender on the occurrence of congenital hypothyroidism specifically with high sample size among different geographical regions and races.

5- CONCLUSION

The results of this meta-analysis provide evidence for a higher risk in girl gender for developing congenital hypothyroidism. More epidemiological and clinical studies are needed to explore why girl gender is at increased risk of congenital hypothyroidism compared with boy.

6- AUTHORS' CONTRIBUTION

All authors contributed equally and participated in the data extraction, analysis and interpretation. All authors critically reviewed, refined and approved the manuscript.

7- CONFLICT OF INTEREST: None.

8-ACKNOWLEDGMENTS

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