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META-ANALYSIS

Universal screening versus selective case-based screening for thyroid disorders in pregnancy

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Abstract Thyroid dysfunction in pregnancy is associated with significant maternal, fetal, and neonatal complications. Early treatment of thyroid disorders can effectively reduce the risk of such complications. The results of different clinical trials have demonstrated that screening pregnant women for thyroid dysfunctions is cost-effective and should be encouraged. However, there is no consensus over the advantages of universal versus case-finding screening for thyroid disorders during pregnancy. A systematic review was performed by searching PubMed, Scopus, and Web of Science databases for studies having been carried out to make a comparison between universal and case-finding screening methods during pregnancy in terms of the loss rate. The main search criteria were related to thyroid function, pregnancy, and adverse outcomes. All articles in English language are included. We analyzed by random effect method due to between-study heterogeneity. Among 241 articles found using the search terms, 40 articles were included out of which 10 were considered as acceptable and relevant. Five articles showed that case-finding screening missed between 30 and 55 % of pregnant women with thyroid dysfunction. 4 studies demonstrated that universal screening and detection of thyroid dysfunction may lead to less miscarriage and pregnancy complications. The results of 2 studies demonstrated that universal screening in pregnancy with a focus on hypothyroidism would be cost-effective. Early detection of thyroid dysfunction in pregnancy can minimize the adverse maternal and fetal outcomes and is demonstrated to be cost-effective. Meta-analysis confirmed that case-based screening may miss up to 49 % of pregnant women with thyroid dysfunction. This provides further support for the argument in favor of universal screening of thyroid disorders in pregnancy. In order to shed more light on the advantages of universal screening for thyroid disorders in pregnancy, more comprehensive randomized controlled trials with larger cohorts are required.

Keywords Thyroid · Pregnancy · Universal screening · Case-finding screening · Meta-analysis · Cost-effective · Systematic review

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Introduction

Thyroid dysfunction has a significant effect on the health of pregnant women, fetus, and neonate. Although some studies have reported contradictory results, [4] it is demonstrated that maternal thyroid dysfunction in pregnancy may affect childhood psychomotor development and lead to a reduction in intelligence quotient [1–3]. In fact, screening for thyroid diseases during pregnancy has been a matter of debate during the recent decades [5].

Overt and subclinical hypothyroidism is associated with both maternal and fetal complications which can be easily

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prevented by means of levothyroxine replacement therapy, thereby reducing the risk of complications. Negro et al. [6] have demonstrated the significant efficacy of levothyroxine treatment in reducing pregnancy complications in euthyroid women. Moreover, findings of Yu et al. [7] indicate that a constant levothyroxine dose can maintain serum TSH levels within the ideal range in 79.3–90 % of patients which may obviate the need for monthly evaluation of thyroid function until the end of pregnancy. Moreover, it is demonstrated that even in euthyroid women, the presence of autoantibodies against thyroperoxidase (TPOAb) can increase the rate of miscarriage and premature birth [8]. Furthermore, up to 50 % of the TPOAb-positive pregnant women are exposed to an increased risk of development of post-partum thyroiditis (PPTD) [9, 10]. In fact, the concept of post-partum rebound of thyroid diseases involves not only autoimmune thyroiditis, but also Graves' disease [11].

Several trials have indicated that screening pregnant women for thyroid dysfunction is both feasible and cost-effective [12, 13]. The American Association of Clinical Endocrinologists (AACE) recommends routine TSH measurement in the elderly patients (age not specified) especially in women [14, 15]. An American Thyroid Association guideline indicates that currently there exists insufficient evidence to support or refute feasibility of preconception TSH testing in women at high risk for hypothyroidism [16]. In 2013, Feldt-Rasmussen [17] attempted to shed some light on the issue without success as their data were insufficient and contradictory. Moreover, the Endocrine Society Clinical Practice Guideline did not reach an agreement on this matter [1]. A study by Vaidya et al. [18] revealed that screening only high-risk pregnant women would miss about 30 % of hypothyroid and 69 % of hyperthyroid women. This report supports the concept of more general and widespread thyroid function screening in pregnant women.

Because of scarcity of the literature which has contributed to contradictory and confusing results, the controversy over universal versus per case screening continues. Therefore, we designed the current systematic review and meta-analysis to compare the efficacy of universal screening versus high-risk case finding in terms of identification of thyroid disorders during pregnancy. This meta-analysis, however, did not evaluate the efficacy of treatment of pregnant women with levothyroxine in decreasing maternal/fetal adverse events in comparison with the pregnant women who were not treated with levothyroxine.

Methods

PubMed, Scopus, and Web of Science databases were searched for studies investigating universal and case-based screening in pregnant women. The main search criteria used were related to thyroid function, pregnancy, and adverse outcomes. Specifically, the following search terms alone or in combination were used: thyroid*,pregnan*,gestation*,matern*, universal screening, case-finding screening, and targeted high-risk case finding. Mesh terms used were thyroid gland, thyroid diseases, pregnancy, pregnancy outcome, and pregnancy complications without narrowing or limiting search items. There were no language limitations for the initial search. Randomized controlled trials (RCTs), cohort studies, and case–control studies were included.

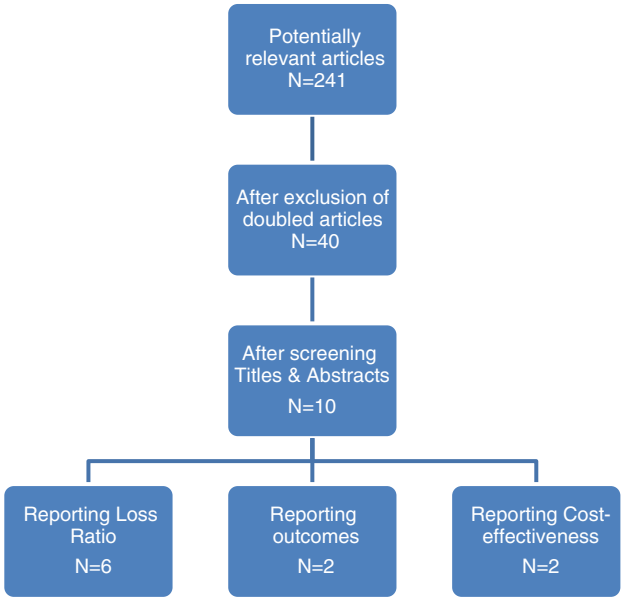

Fig. 1 Flow chart of literature search and article selection

Publications with available English abstracts were reviewed. Data were collected according to a standard protocol independently by two authors. Disagreement was resolved by discussion between them. All articles without any limitation for time of publication were identified and studies carried out on pregnant women were included. The included articles based on the expert panel guidelines labeled pregnant women who had a personal or family history of thyroid disorder or a personal history of other autoimmune disease as high-risk groups.

Articles which were not identified as relevant after full text evaluation were excluded. We assessed the quality of each study and extracted information regarding its setting, patients, interventions, and outcomes. Publication details of studies with the main outcome of thyroid dysfunction and Thyroid screening in pregnancy were assessed for title duplication and they were eliminated. Figure 1 shows the flow chart of literature search and article selection. Only studies reporting the loss ratio were included for

Table 1 The characteristics of included studies sample size, TSH and TPOAb cutoff values, and Loss ratios

Study	SStudy design	Sample size	TSH reference range	TSH cutoff	Thyroid dysfunction	TPOAb cutoff	TPOAb positive	Loss ratio	Outcome change
Wang et al. [19]	Multicenter Cohort	2,899	0.13–3.93 mIU/L	>3.93 mIU/L	Total: 294(10.2 %) Hyperthyroidism: 1.8 % Hypothyroidism: 7.5 % Hypothyroxinemia: 0.9 %	≥50 IU/ml	279(9.6 %)	Total: 80.8 % 81.6 % (Hypo) 80.4 % (Hyper)	0.9 % Affect neuropsychological development
Matuszek et al. [20]	Case–control	270	0.5–4.5 mIU/L	>2.5 mIU/L	Hypothyroidism: 10.4 %	–	71.4 %	46.4 %	–
Goel et al. [21]	Prospective case–control	1,020	0.6–5.0 IU/mL	>2.5 IU/mL	Hypothyroidism: 6.3 %	>80 kIU/L	–	32 %	27.6 % greater gestational Htn, 65 % required induction in overt hypothyroid group NS difference in the incidence of fetal distress or Apgar score
Vaidya et al. [18]	Single-center cohort	1,560	0.27–4.2 mIU/L	>4.2 mIU/L	Low risk: 1 % raised TSH High risk: 6.8 % raised TSH	–	Nl TSH:79.4 % Raised TSH:13.5 % Low detectable TSH:4.8 % Fully suppresses TSH: 2.4 %	30 %	–
Horacek et al. [22]	Cross sectional	400	0.15–5.0 mIU/L	>3.5 mIU/L	10.3 % raised TSH (16.3 % at least one abnormality)	>50 IU/L	8.3 %	55 %	–
Lepoutre et al. [24]	Retrospective descriptive study/case control, Interventional	823	0.2–3.5 mIU/L	>1 mU/L	–	>9 U/mL	17.8 % (96/537)	–	A sig. difference of 16 % miscarriage rate between treated & nontreated group No other sig. differences such as gestational Htn. Or DM

Table 1 continued

Study	SStudy design	Sample size	TSH reference range	TSH cutoff	Thyroid dysfunction	TPOAb cutoff	TPOAb positive	Loss ratio	Outcome change
Negro et al. [25]	Cross sectional/ interventional	4,562	0.27–4.2 mIU/L	>2.5 mIU/L	Case-finding High risk: 95.2 % euthyroid,4.4 % hypo, 0.4 % hyper) (Case-finding Low risk: 97.9 % euthyroid.1.9 % Hypo, 0.2 % Hyper) (Universal screening: 96.8 % euthyroid, 2.8 % Hypo, 0.4 % Hyper)	>100 kIU/L	(Case finding euthyroid Ab+:5.7 % Universal screening euthyroid Ab+:5.8 %	–	2.48 % fewer adverse events by screening low-risk women/No decrease in adverse outcomes by universal screening
Jiskra et al. [23]	Prospective Cross sectional	5220 (200 positive in screening)	0.06–3.67 mIU/L	>3.67 mIU/L	21 % TGH, 5 % overt hypothyroidism, 38 % subclinical hypothyroidism, 3.5 % hyperthyroidism, 33 % euthyroid	>143 kIU/L	63 %	Less than 50 % (47 %)of the positively screened pregnant women can be classified as high risk	–

Htn hypertension, *NS* not significant, *Sig* significant, *DM* diabetes mellitus, *TGH* transient gestational hyperthyroidism

Table 2 The loss ratios reported by included trials

Study	Study design	Loss ratio (%)	ES (95 % CI)
Wang et al. [19]	Case finding	80.8	0.81 (0.79, 0.83)
Matuszek et al. [20]	Case finding	46.4	0.46 (0.37, 0.56)
Goel et al. [21]	Case finding	32	0.32 (0.25, 0.39)
Vaidya et al. [18]	Case finding	30	0.30 (0.23, 0.37)
Horacek et al. [22]	Case finding	55	0.55 (0.48, 0.62)
Jiskra et al. [23]	Universal screening	47	0.49 (0.24, 0.74)

meta-analysis. Loss ratio was defined as the percentage of cases of hypothyroidism, which were missed by means of case-finding screening. After a consensus was reached, the remaining articles were included for critical appraisal and assessed by two reviewers independently. Articles in foreign languages were translated and included if they met the inclusion criteria except for articles in Chinese, Japanese, Czech, and Russian. We analyzed our findings using meta-analysis random effect methods model (using the DerSimonian and Laird method) analysis due to the presence of between-study heterogeneity.The analyses were conducted with the use of STATA software, version 11.0.

Result

Among 241 articles found by our search terms, 40 articles were included for the review based on their title, relevancy, and abstracts. Finally, 10 eligible articles were selected and included.

Finding of five articles showed that case-finding screening would miss between 30 and 55 % of pregnant women with thyroid dysfunction [18–22] and only one study did not support the feasibility of universal screening in pregnant women [23]. All studies showed that the prevalence of thyroid dysfunction (especially hypothyroidism) was higher in the group of pregnant women with risk factors for thyroid disease.

Four studies showed that universal screening followed by detection and treatment of thyroid dysfunction during pregnancy may lead to reduced miscarriage rate and fewer pregnancy complications including gestational hypertension, as well as reduced neuropsychological development deficits [19, 21, 24, 25]. Details of the findings are tabulated in Table 1.

As the Chi square for heterogeneity test showed that the data were heterogenic ($p < 0.001$), random effect model was used to analyze data from the five included studies. The results of the analysis showed that overall loss ratio in case-finding method was 49 % (CI 0.23–0.74). Details are shown in Table 2 and Fig. 1.

One study on universal screening showed that less than half of the women with positive pregnancy tests could be classified as high risk [23].

The findings of two different studies demonstrated that universal screening for hypothyroidism and autoimmune thyroid disease in pregnancy would be cost-effective [13, 26]. In this regard, Thung et al. [26] reported an 8,356,383 $ saving using a model of 100,000 pregnant women which gained 589.3 QALYs. Moreover, Dosiou et al. [13] concluded that Universal screening was more cost-effective in comparison with risk-based screening with an ICER (Incremental cost- effectiveness ratio) of $7,258/QALY.

Discussion

Thyroid dysfunction during pregnancy is common and leads to adverse pregnancy and perinatal outcomes. On the other hand, the efficacy of LT4 treatment during pregnancy to decrease adverse outcomes is controversial which is at the heart of controversy regarding universal screening.

Casey et al. [27] in 2005 concluded that pregnant women with subclinical hypothyroidism experienced 3 times higher complicated pregnancies.

Due to the importance of thyroid dysfunction in pregnant women, we reviewed 8 articles comparing universal screening versus case-finding screening during pregnancy. Five studies [18–22] reported that case-based screening for the detection of thyroid dysfunction during pregnancy can result in failure to detect 81, 46.4, 32, 30, and 55 % of pregnant women with thyroid dysfunction. Figure 2 shows the loss ratio of each article.

Wang et al. [19] showed that the prevalence of hypothyroidism was significantly higher in the high-risk group of pregnant women. The study found that testing only high-risk pregnant women for thyroid dysfunction failed to detect 81.6 % pregnant women with hypothyroidism and 80.4 % pregnant women with hyperthyroidism in the high-risk group. Among all articles that reviewed, Wang et al. [19] reported the highest loss ratio although four studies [18, 20–22] also indicated the loss to lower extents (46.4, 32, 30, and 55 %). All the five mentioned studies used case-based strategy to screen for thyroid dysfunction in pregnant women. Goel et al. [21] showed that screening pregnant women for thyroid dysfunction as recommended by the US Preventive Services Task Force [4] can fail to detect nearly one third of pregnant women with hypothyroidism. However, in this study, the maternal and fetal outcomes were comparable in treatment and control group.

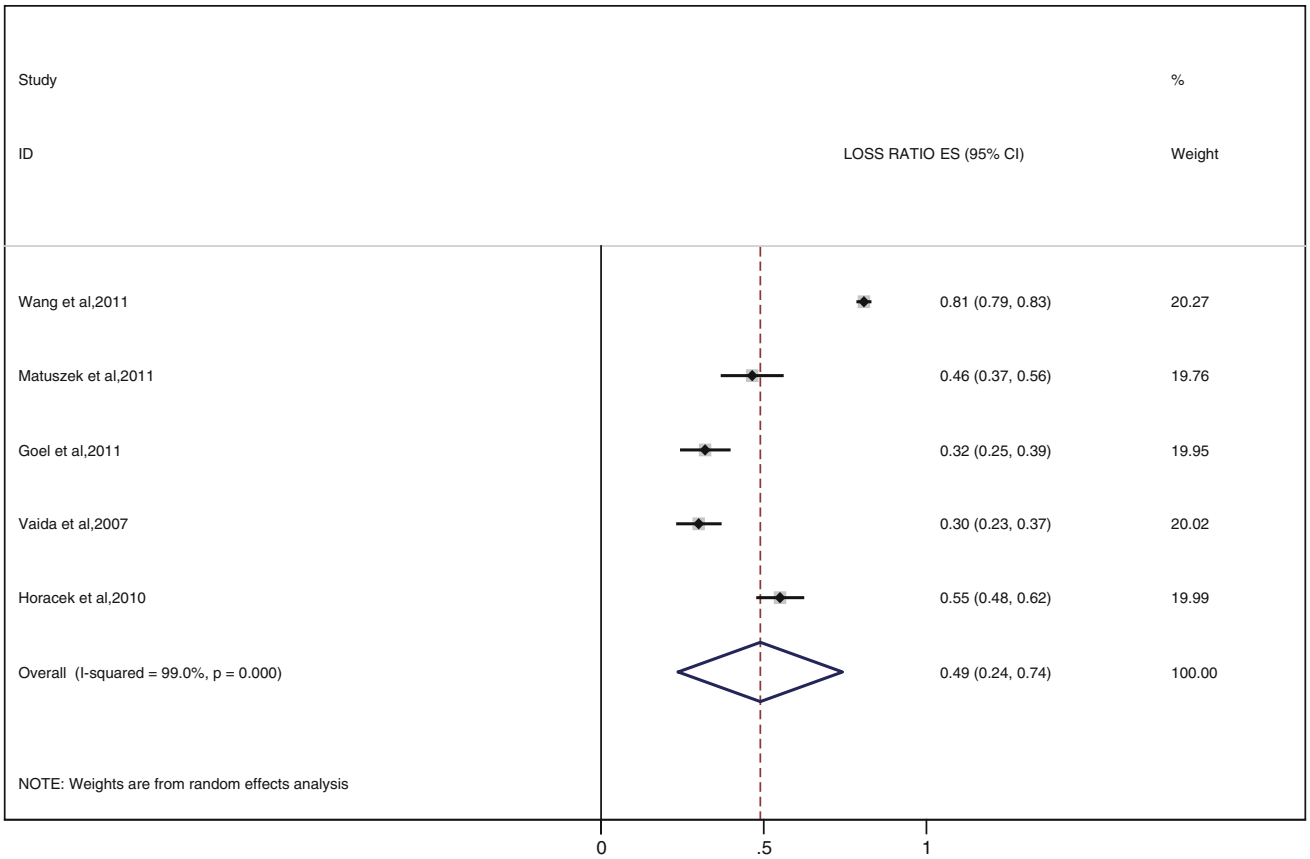

Fig. 2 Graph of loss ratio reported by eligible articles

Findings of both Matuszek et al. [20] and Horacek et al. [22] indicate that if only high-risk criteria are used, case-based screening in pregnancy can result in failure to detect nearly 50 % of the cases.

Different TSH values as well as higher and lower cutoffs were used in the study design of the mentioned articles. Matuszek et al. [20], Goel et al. [21], and Negro et al. [25] recommend lower TSH values for detecting hypothyroidism (to a level below 2.5 mIU/L) in the first trimester of gestation according to the recommendations of the 2007 Endocrine Society Clinical Practice Guideline [28]. Some studies, however, emphasize on using trimester-specific reference ranges rather than general population references intervals to avoid misdiagnosis during pregnancy [1, 18, 19].

Jiskra et al. [23] concluded that universal screening was not superior as less than half of the positively screened pregnant women can be classified as high risk, which is not significant.

On the other hand, some studies have found increased adverse outcomes in children of pregnant women with thyroid dysfunction such as decreased IQ and intellectual impairments [3, 29, 30]. In this review, two studies carried out by Negro et al. [25] and Lepoutre et al. [24] investigated the adverse effects rates between pregnant women screened by one of universal or case-finding methods. Negro et al. in a randomized trial study of 4,562 pregnant women reported that universal screening did not result in a decrease in adverse outcomes in comparison with case-finding method. However, the case-based strategy failed to detect the majority of pregnant women with thyroid diseases, and therefore, he recommended a comprehensive cost-effectiveness analysis to resolve this controversy [25]. Moreover, Lepoutre et al. (in a case–control study of 823 pregnant women) evaluated the rate of miscarriage and other adverse outcomes through universal and case-finding screening. Their conclusion supports the potential benefits of early universal thyroid screening in reduction of pregnancy adverse outcomes [24]. However, despite the conclusive findings of the mentioned two studies, currently, except for the American Thyroid Association, universal screening is not recommended by any medical society [16]. It is noteworthy that a clinical trial designed by Lazarus et al. [4] for evaluation of the effect of routine antenatal screening for hypothyroidism in pregnancy on offspring provided support for the mentioned guideline. In 2012, the members of the Endocrine Society could not reach an agreement for the implementation of

screening for all pregnant women, although some members recommended screening of all pregnant women by the 9th week or at the first visit for pregnancy [1].

Finally, we reviewed two articles evaluating the cost-effectiveness of universal screening for thyroid diseases in pregnancy. Both of them concluded that universal screening was a cost-effective strategy in pregnant women [13, 26]. Doisu et al. [13] showed that universal screening was cost-effective in comparison with no screening with incremental cost-effectiveness ratios (ICERs) of $7,138/QALY. This result was also confirmed by Thung et al. [26], which reported that a universal TSH screening program could result in a cost savings of $8,356,383. The results of these two studies are consistent with other cost-effectiveness studies regarding the thyroid function screening in non-pregnant women and general population [31, 32].

Possible limitations in our study include not using a standard quality assessment scale for evaluating the articles and the need for large-scale trials revolving around this topic.

In conclusion, early detection of thyroid dysfunction in pregnancy may minimize adverse maternal and fetal outcomes and has been shown to be cost-effective. Meta-analysis has shown that case-based screening can miss up to 49 % of pregnant women with thyroid dysfunction. This provides further support for advocacy of universal screening methods for thyroid disorders in pregnancy. Further comprehensive randomized controlled trials are needed to shed more light on this controversial topic.

Conflict of interest The authors declare that they have no conflict of interest.

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