Review Article

Controversial Screening for Thyroid Dysfunction in Preconception and Pregnancy: An Evidence-Based Review

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Abstract

Objective: To evaluate the recommendations on the most adequate screening method (universal or selective) for thyroid dysfunction. Although thyroid dysfunction is a common disorder in fertile women and untreated cases may have negative maternal, fetal and neonatal outcomes, its screening in preconception and early pregnancy is controversial.

Materials and methods: An evidence-based review was conducted to identify publications since 2017 of American Thyroid Association (ATA) guidelines, according to the following Population, Intervention, Comparison, Outcomes and Study (PICOS): women in preconception or pregnancy without thyroid disease who underwent universal or selective screening for thyroid dysfunction. Study selection obeyed the PRISMA criteria.

Results: We included 15 of 325 publications. The 2017 ATA guidelines recommend selective screening in both preconception and pregnancy. The only two reviews on preconception recommended universal screening. For pregnancy, nine articles suggested universal screening, while a prospective study advocated selective screening. The main benefits advocated for universal screening were easy and low-cost tests; absence of missed diagnosis; safe and inexpensive treatment and its potential in preventing negative outcomes. Iodine deficiency is a decisive indication, but it was not evaluated in all clinical studies. Screening harms and knowledge gaps were the main arguments against universal screening. There are very few cost-effectiveness studies.

Conclusion: We recommend universal screening for thyroid dysfunction in early pregnancy, which is a distinct point of view from 2017 ATA guidelines (weak recommendation, low-quality evidence). It is not possible to make a formal recommendation for preconception (insufficient evidence). We strongly suggest an individualized analysis by each country.

Keywords: Screening; Thyroid Function; Preconception; Pregnancy; Endocrinology; Primary Health Care; Maternal Health

Introduction

Thyroid dysfunction is common among women of reproductive age. In pregnancy, it is estimated an incidence of 0.3-0.5% for overt hypothyroidism, 3-5% for subclinical hypothyroidism and 0.1-0.4% of hyperthyroidism (1). It is well established that overt thyroid disorders have a negative impact on

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pregnancy and they must be managed with appropriate therapy, aiming at rapid achievement of euthyroidism (2). The effects and outcomes of subclinical hypothyroidism have been questionable, as indications for levothyroxine treatment and its impact on maternal and fetal health are not unanimous in studies with distinct methodological criteria (3-5).

Studies on subclinical hypothyroidism have emerged, revealing the potential to adversely impact maternal and fetal outcomes. Untreated cases have been associated with a higher risk of preeclampsia, prematurity, low birth weight and neonatal respiratory distress syndrome (6, 7). Furthermore, multiple studies have shown that thyroid peroxidase antibody (TPOAb) positivity could be an important factor of negative pregnancy outcomes in women with subclinical hypothyroidism or even in euthyroidism (thyroid stimulating hormone [TSH] ≥ 2.5mIU/L) (2, 8-10). Consequently, 2017 ATA guidelines provided a brand-new recommendation to take into consideration the TPOAb status in women with TSH ≥ 2.5 mIU/L during preconception and pregnancy to support the decision on the need of levothyroxine treatment (2).

Considering that untreated subclinical hypothyroidism can be associated with negative maternal, fetal and neonatal outcomes (11), and that the treatment with levothyroxine has demonstrated to reduce their occurrence in TPOAb-positive women with subclinical hypothyroidism (10, 12), it is essential to discuss and achieve concrete screening tactics in preconception and the early stage of pregnancy, since currently there is significant controversy regarding the screening of thyroid dysfunction in both phases (3, 13).

This evidence-based review aims to evaluate the most adequate screening method (universal versus selective) of thyroid dysfunction in preconception or early pregnancy in women without known thyroid disease through TSH levels assessment and, when available, the measurement of free thyroxin (fT4). It seeks to identify all relevant studies on this topic and to evaluate them in a qualitatively manner based on explicit criteria.

Materials and methods

Type of study: This is an evidence-based review, which methodological concept includes choosing a common and important clinical problem in Family Medicine and searching the topic on several sources of literature. After applying inclusion and exclusion criteria, we evaluated the strength and validity of the literature that supports the discussion of our article.

Eligibility criteria: We pre-specified eligibility criteria using the population, intervention, comparison, outcomes and study design (PICOS) approach. We defined the following PICOS:

- Population (P): women in preconception or early pregnancy without known thyroid disease;
- Intervention (I): universal evaluation of TSH level (and TPOAb and fT4 level, when available);
- Comparator (C): selective evaluation of TSH level (and TPOAb and fT4 level, when available);
- Outcome (O): detection of thyroid dysfunction through TSH level out of reference range (and TPOAb and fT4 level, when available);
- Study Design (S): evidence-based review, which includes the analysis of classic reviews, prospective studies, cross-sectional studies, national guidelines and commentary/expert opinions.

Studies that commented on the screening methods for thyroid dysfunction by TSH assessment during preconception or early pregnancy of healthy women, namely without known thyroid disease, were included. Exclusion criteria were studies aimed only to evaluate the normal range of TSH or thyroid dysfunction treatment or its impact on maternal and fetal outcomes, as well as those studies that included women treated with levothyroxine or antithyroid drugs and cases of multiple or assisted pregnancies. Case reports and guideline summaries were not considered. Only articles written in English or Portuguese were included.

Eligibility assessment was determined independently by two authors. In case of disagreement, the authors re-evaluated the paper together and came to a mutual decision.

Information sources and search strategy: On June 15, 2019, a literature search was conducted to identify articles published since January 1, 2017, year of publication of the "2017 Guidelines of the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum" (2), by using PubMed (MEDLINE), Cochrane Collaboration, Canadian Medical Association Practice Guidelines InfoBase, Bandolier, DARE and Evidence Based Medicine online. All records were screened for relevant titles or abstracts independently by two authors.

Study selection: Considering the maintained controversy of this theme for maternal and fetal

health and the existence of sparse data over the years, the authors of this study decided to include several study designs. Although, due to the lower level of evidence, the authors decided to include expert opinions. Classic literature reviews, prospective and cross-sectional studies, national guidelines and expert opinions relevant to the topic were selected and assessed to justify a performance of an evidence-based review.

After initial research, we opted for the query "Thyroid screening AND (Pregnancy OR Conception)". Selection of studies obeyed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria. The selected articles were evaluated independently by two authors according to the Strength of Recommendation Taxonomy (SORT) from American Academy of Family Physicians to classify the level of evidence and assign the strength of the recommendation, following discussion and consensus.

The validity of an individual study is based on the assessment of its study design. This approach takes into account the level of evidence of individual studies, the type of outcomes measured by these studies (patient-oriented or disease-oriented), the number, consistency and coherence of the evidence as a whole, and the relationship between benefits, harms and costs.

Data collection process: Information was extracted from each included manuscript on: 1) characteristics of study (type of study, level of evidence; for classic reviews, the number of articles included; for prospective and cross-sectional studies, laboratory measurements for thyroid dysfunction screening, arms of the study and their risk of having thyroid dysfunction (low versus high) and the length of recruitment); 2) characteristics of participants for prospective and cross-sectional studies (number of cases, age and time of pregnancy); 3) outcomes (phase of screening (preconception or early pregnancy); recommended screening method (universal versus selective) and main points of view).

Considering individual laboratory cut-offs, overt hypothyroidism was defined as increased TSH and low fT4 levels. Subclinical hypothyroidism was defined as increased TSH levels associated with normal fT4.

Beyond the analysis of the considerations on the screening methods of thyroid dysfunction, the authors also reviewed the applicability of the arguments and recommendations of the publications in the Portuguese population.

Prior to conducting this evidence-based review, authors established the selection criteria and research project. The authors did not create or register a specific protocol for this review, following the methods described above.

Results

Study selection: We identified 325 manuscripts from the different databases after the removal of duplicates. Of these, 261 were excluded by title, 1 by language, 34 after reading the abstract. Of these, 29 were full-text screened for eligibility. We had direct access to the full text of all remaining papers, so no authors had to be contacted. Of the remaining papers, 14 were excluded after reading the full article according to the aforementioned inclusion and exclusion criteria. Finally, we identified 15 eligible publications for our analysis, all in English.

Study characteristics: Of 15 manuscripts included, we identified six classic literature reviews (3, 14-18), three prospective studies (19-21), two cross-sectional studies (22, 23), one guideline (2) and three expert commentaries (4, 13, 24). Four publications presented a level of evidence of one (19-22), six manuscripts of two (3, 14, 16-18, 23) and four manuscripts of three (4, 13, 15, 24). Only three manuscripts analyzed the most adequate screening method in preconception (2, 14, 15), while thirteen articles evaluated the screening during pregnancy (2-4, 13, 16-24).

Classic literature reviews comprised a total of 393 articles. Prospective and cross-sectional studies examined 5758 pregnant women, with a mean age by paper between 25.4 and 31.0 years old. The majority of the studies included first trimester pregnant women (19, 20, 22, 23) and one study included women up to 34 weeks pregnant (21). The duration of the recruitment varied from 11 to 24 months (20, 22, 23).

Two studies (one prospective and one cross-sectional) (19, 23) divided pregnant women in three arms (random, high and low risk) and two arms (high and low risk), respectively. The other three studies evaluated all the participants together (20-22), one of them defining its sample as a low-risk group (21). Not all the publications explained the criteria of the risk for thyroid dysfunction or used the same criteria. High risk was defined by Rosario PW and Sitoris et al. according to 2017 ATA's criteria for selective screening (21, 23). However, Sitoris et al. considered as additional risk factors a body mass index above 25 kg/m^2, Caucasian background and iron deficiency (23). On the other hand, two publications that evaluated all the participants together excluded some

high-risk women. Pop et al. excluded women with a known history of autoimmune disease (diabetes mellitus, rheumatoid arthritis) and Akter et al. excluded patients with a family history of thyroid disease (20, 22). Three of five studies did not perform a comparative evaluation between arms (20-22) and two studies did not describe specifically the risk of the sample of having thyroid dysfunction (20, 22).

Measurement of TSH, fT4 and TPOAb were performed in one prospective study and two cross-sectional studies (20, 22, 23), while TSH and TPOAb assessment occurred in one prospective study (21) and TSH measurement alone was done in another one (19). Regarding the iodine status of the participants in prospective and cross-sectional studies, Pop et al. and Rosario PW included healthy pregnant women from an iodine-sufficient area. Akram et al., Akter et al. and Sitoris et al. have not considered the iodine status of the participant women (19-21).

Results of individual studies: Currently, "2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum" are the international recommendations most used by clinicians in this context (2). This publication referred that:

1. During preconception: there is insufficient evidence to recommend for or against the universal screening for TSH alterations - no recommendation, except if positive for TPOAb or in case of planning assisted reproduction;
2. During early pregnancy:

- There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations - no recommendation.
- Universal screening to detect low fT4 concentrations is not recommended - weak recommendation.

American Thyroid Association also recommended that all women in preconception or early pregnancy should be clinically evaluated. Women with known thyroid disease (including history of hypothyroidism or hyperthyroidism, thyroid antibody positivity, head and neck radiation or prior thyroid surgery) indicate thyroid function screening. Furthermore, ATA strongly recommended a selective screening with TSH, both on preconception and early pregnancy, in the following situations applicable in women without known thyroid disease, with a moderate level of evidence (2):

- Current symptoms or signs of thyroid dysfunction;
- Presence of goiter;
- Age over 30 years;
- Type 1 diabetes mellitus or other autoimmune disorders;
- History of pregnancy loss, preterm delivery or infertility;
- Multiple prior pregnancies (equal or higher than 2);
- Family history of autoimmune thyroid disease or thyroid dysfunction;
- Morbid obesity (body mass index equal to or higher than 40 Kg/m^2);
- Use of amiodarone or lithium or recent administration of iodinated radiologic contrast;
- Residing in an area of known moderate to severe iodine insufficiency.

Since the publication of the 2017 ATA guidelines, several publications on the topic have emerged, many of them as their critical reflections.

In preconception, in opposition to "no recommendation" of universal screening by the ATA due to insufficient evidence (2), Kalra et al. suggested that screening for thyroid disorders is indicated for all women as part of preconception counselling (15), as Maheshwari et al. argued that universal screening for alteration of TSH levels can be cost-effective, particularly in iodine deficient areas (14).

During pregnancy, on the one hand, Rosario PW evaluated women up to 34 weeks gestation and concluded that selective screening does not significantly exclude pregnant women with an indication for levothyroxine treatment (21). On the other hand, Martinez et al., Alex Stagnaro-Green, Velasco and Taylor, Akram et al., Akter et al. and Sitoris et al. suggested universal screening because they consider that selective evaluation of high risk groups excludes pregnant women at risk of thyroid dysfunction in early pregnancy (3, 4, 16, 19, 22, 23).

Velasco and Taylor advocated a universal screening approach for pregnant women in Europe (16), considering that most countries are iodine deficient, unlike the United States of America (USA) where ATA recommends selective screening (2). Springer et al. and Taylor et al. presented pros and cons of selective and universal screenings (17, 18). The first one did not make any formal recommendation (17), but the second recommended universal screening due to its cost-effectiveness (18). Pop et al. discussed the utility of the ATA selective criterion of thyroid dysfunction symptoms to identify high-risk pregnant women, because symptoms are too difficult to evaluate during pregnancy (20). Martinez et al. indicate the need for further studies to establish clear and strong recommendations about screening for thyroid dysfunction in pregnancy (3), that is a

generalized perspective of most of the included articles (13, 14, 17, 19, 20). This is also demonstrated in a survey among Endocrinologists and Obstetricians/Gynaecologists (24), with no clear consensus regarding universal or selective screening in preconception and early pregnancy.

The most important data of each manuscript, except for ATA guidelines, (2) are presented in Table 1.

Summary of main findings: American Thyroid Association guidelines declare not to have a formal recommendation on the most adequate screening method for thyroid dysfunction, both in preconception and in pregnancy, due to insufficient evidence (2). Throughout this section, ATA defends that TPOAb-positive women, planning assisted reproduction or presenting one of the listed conditions should perform the screening. In this way, ATA recommended selective screening in both phases.

Differently, for preconception, two classic reviews recommended universal screening (14, 15). For pregnancy, nine articles suggested universal screening (3, 4, 16-19, 22-24). A prospective study, the only one including women beyond the first trimester of pregnancy, advocated selective screening. The remaining publications did not establish a recommendation during pregnancy (13, 20). These articles indicated the need for further studies, which is a common viewpoint of most authors.

Discussion

In the last decade, data has provided a perplexing dilemma about whether all women or only a high-risk group should be screened for thyroid dysfunction in preconception and pregnancy. To the best of our knowledge, our paper is the first evidence-based review on the best screening method for thyroid dysfunction (selective versus universal) in preconception and early pregnancy. The careful analysis of the included publications revealed no good-quality evidence for the preconception period and reasonable quality evidence in early pregnancy.

Screening considerations: One of the most discussed points on the best screening method is the possibility of exclusion of a sizeable number of women at risk of thyroid dysfunction in case of selective evaluation of high-risk groups, compared to universal screening. This position has been highlighted by the most recent publications that favour universal screening, contrary to Rosario PW (3, 4, 16, 18, 19, 21, 23). Universal screening removes the risk of missing women with thyroid dysfunction, with variable proportions but that can reach a prevalence of 40% in pregnancy (23). Furthermore, a significant number of thyroid dysfunction cases could be labelled as low risk, as demonstrated by Akram et al., a prospective study that found a similar prevalence of subclinical hypothyroidism among groups with different risks (19). In positive cases at screening, pregnant women have to be referred to a specialist for adequate management that could include eventually further investigation such as TPOAb measurement. The treatment of women with criteria was shown to prevent adverse outcomes (10, 12) and the risk of low dose of levothyroxine is irrelevant. In addition to not excluding women with thyroid dysfunction and reducing negative outcomes, there are also other important benefits of universal screening, since thyroid dysfunction during pregnancy can be considered a health problem and that its screening consists in a reliable and low cost blood test (18, 25). However, a universal approach can be unnecessary in many countries where there are no cost-effectiveness studies. For the pregnant women, the need for screening as soon as pregnancy is confirmed could be a stressful situation. However, it must occur very early in pregnancy (about 4-7 weeks gestation) to maximize the benefits of levothyroxine treatment regarding fetal neurodevelopment and pregnancy loss rates (2). In fact, the mother is the only source of thyroid hormones, which are critical in neurocognitive development, until fetal thyroid gland becomes physiologically active in the second half of the first trimester.

The controversial results of studies in this area can be mainly due to different methodologies. Despite the multiple studies, they include pregnant women with variable gestation age at the time of the screening, some of them even in the third trimester. It is important to note that probably the controversy about the truly impact of the treatment of pregnant women with subclinical hypothyroidism is associated with the late start of levothyroxine.

Laboratory parameters are another relevant point. Maternal TSH is a very sensitive marker of thyroid dysfunction and, undoubtedly, it is mandatory in the screening. In contrast, the measurement of fT4 has technical limitations of the immunoassay due to transporter proteins. Peripheral levels of TSH and fT4 change throughout pregnancy depending on several factors such as timing of gestation, maternal iodine status and the measurement technique (3). So, thyroid function assessment is recommended on the basis of trimester-specific reference intervals for each laboratory/population (1, 2).

Table 1: Position of each paper about the most adequate screening method in preconception or pregnancy

Article and type of study	Recommended screening method	Point of view	LE
Maheshwari et al.(14) Classic review (27 articles)	Preconception: universal	Selective screening can exclude a large proportion of women with increased TSH level and it is not cost-effective when compared to universal screening. Universal screening may be cost-effective, particularly in iodine deficient areas, but there is no large-scale data of screening all women in preconception.	2
Kalra et al.(15) Classic review (6 articles)	Preconception: universal	Keeping in view the high prevalence of subclinical hypothyroidism, iodine deficiency and lack of universal iodized salt use, biochemical screening for thyroid disorders should be a mandatory part of preconception care. Screening for thyroid disorders, using a sensitive and accurate TSH assay, is indicated for all women as part of pre-conception counselling.	3
Martinez et al.(3) Classic review (56 articles)	Pregnancy: Universal	The analysis of the current evidence allows assuming that the implementation of a systematic screening of thyroid function in the first trimester of pregnancy provides a more efficient way to detect gestational thyroid dysfunction. However, there are difficulties of interpretation and management in clinical practice.	2
Velasco and Taylor(16) Classic review (92 articles)	Pregnancy: Universal	Universal screening is cost-effective. Selective screening of high-risk women will lead to a loss of many cases of thyroid dysfunction. Most European countries are iodine deficient, unlike the United States of America, so the implementation of ATA 2017 should take this into account. Before recommending a screening policy, agreement should be reached on management between endocrinologists and obstetricians of thyroid disease in pregnant women.	2
Springer et al.(17) Classic review (147 articles)	Pregnancy: Universal	Thyroid dysfunction evaluation should be done in women with high risk and, according to some authorities, in all pregnant women. Several entities recommend universal screening and there is no evidence this practice is cost-effective.	2
Taylor et al.(18) Classic review (65 articles)	Pregnancy: Universal	Screening in high-risk patients appears to miss the majority of cases and economic models show that universal screening with TSH and TPOAb during the first trimester is cost-effective. There is a need for specific reference ranges of TSH for pregnant women.	2
Akram et al.(19) Prospective study 1298 pregnant women (random, low risk and high risk groups)	Pregnancy: Universal	Selective screening of high risk groups excludes women at risk of having thyroid dysfunction in early pregnancy, as they found a similar prevalence of subclinical hypothyroidism (TSH $\geq$ 2.5 mIU/L) among the 3 groups (random 9.8% vs low risk 9.6% vs high risk 10.2%, p = 0.948). Universal screening may be appropriate once the pregnancy is confirmed.	1
Pop et al.(20) Prospective study 2198 12-week pregnant women	Pregnancy: none	Of the 15 pregnant women with apparent symptoms, only one required treatment with levothyroxine. It does not support ATA guidelines that pregnant women who need treatment with levothyroxine can be identified by screening women with symptoms of thyroid disease. Signs and symptoms at an early stage of pregnancy do not detect pregnant women at risk for thyroid disease and should not be a screening criterion.	1
Rosario PW(21) Prospective study 412 low risk pregnant women	Pregnancy: Selective	Selective screening according to ATA guidelines does not result in a significant loss of pregnant women with indication for treatment with levothyroxine (none had indication and in two women it could be considered).	1

Table 1: Position of each paper about the most adequate screening method in preconception or pregnancy (continue)

Article and type of study	Recommended screening method	Point of view	LE
Akter et al.(22) Cross-sectional study 186 1st trimester pregnant women	Pregnancy: Universal	25.8% of the women had thyroid dysfunction; 21.5% subclinical hypothyroidism, 0.5% overt hypothyroidism and 3.8% hyperthyroidism; 21.5% women had goitre. It recommends screening all pregnant women regardless of the risk factors.	1
Sitoris et al.(23) Cross-sectional study 1663 pregnant women divided in a high or low risk group	Pregnancy: Universal	Universal screening appears to be the most reasonable approach. Targeted high-risk case finding was not effective for the detection of subclinical hypothyroidism (42% of women with indication of levothyroxine would be missed) but performed better for overt hypothyroidism.	2
Stagnaro-Green(4) Commentary/ Expert opinion	Pregnancy: Universal	The fact that subclinical hypothyroidism (TSH ≥ 2.5 mU/L) with TPOAb positivity is not a clear indication for treatment with levothyroxine, it is not a reason not to track all pregnant women. Selective screening of high-risk groups tends to exclude pregnant women in risk of thyroid disease during early pregnancy.	3
Korevaar(13) Commentary/ Expert opinion	Pregnancy: None	There is insufficient evidence to recommend universal screening. There is no evidence on how to optimally identify women at risk or on the benefits and harms of levothyroxine. Further studies are needed.	3
Koren et al.(24) Commentary/ Expert opinion	Pregnancy: Universal	Questionnaires to 90 ENDO and 42 OB/GYNs: 57% Endocrinologists and 71% OB/GYNs recommend screening every woman at the beginning of pregnancy; 52% of Endocrinologists and 48% OB/GYN recommend screening every woman in preconception.	3

Legend: ATA, American Thyroid Association; LE, Level of evidence; ENDO, Endocrinologists; OB/GYNs, Obstetricians and Gynaecologists; TPOAb, Thyroid peroxidase antibodies; TSH, thyroid stimulating hormone

In case they are not available, TSH reference interval for each trimester should be adapted, as defined by 2017 ATA guidelines (2). Regarding the included studies of this review, Akram et al. and Sitoris et al. used population- and first trimester cut-off levels of TSH and Pop et al. and Akter et al. adjusted them for the first trimester according to ATA guidelines (19, 20, 22, 23). Rosario PW used a TSH reference range which were not specific to pregnant women (21). The absence of population and trimester-specific reference intervals for TSH during pregnancy may not classify correctly maternal thyroid status and can trigger a risk of under or overtreatment. Furthermore, even after 2017 ATA guidelines, the majority of studies did not include TPOAb in addition to TSH. Therefore, they do not include in their results euthyroid women with TPOAb positivity, in whom treatment with levothyroxine should be considered if TSH ≥ 2,5 mIU/L. As well, the cases of isolated hypothyroxinaemia (normal TSH and low fT4) are missed if fT4 is not measured. However, universal screening including also fT4 assessment goes beyond the concept of a screening, aiming a clear diagnosis (26).

Possibly due to the limitations mentioned, significant knowledge gaps exist. The lack of high quality data regarding the negative outcomes of subclinical hypothyroidism and regarding an effective treatment which undoubtedly avoids these adverse outcomes represents a point that needs to be better scrutinized (18).

Iodine deficiency: An important key in the decision for universal screening is the iodine status of the geographical area, considering that it could justify the implementation of universal screening for thyroid dysfunction in areas with moderate to severe iodine deficiency. Most of the included reviews commented on this importance (14-18). Kalra et al. argued that iodine deficiency could be particularly decisive in the implementation of universal screening in the absence of iodine supplementation strategies (15). Half of the included prospective and cross-sectional studies in this review have not considered the iodine status of the participants (19, 22, 23).

Worldwide, iodine deficiency is the most common cause of thyroid disorder and it is the leading cause of preventable intellectual deficits (2, 27). Iodine is a crucial component of thyroid hormones, but it cannot be formed by the human organism. Inadequate iodine intake can cause impaired thyroid hormone synthesis (28). Moderate to severe iodine deficiency can lead to overt or subclinical hypothyroidism and goiter, apparently in people with some extent of thyroid autoimmunity or due to iodine downregulation of thyroid function (29). Thyroid hormones are essential for fetal and neonatal neurodevelopment. Considering that the mother is the only source of iodine for the foetus, mild to moderate deficiency can cause attention deficit, hyperactivity disorders and impaired cognitive outcomes. Severe cases have been associated with impaired mental function, endemic cretinism and increased infant mortality (29).

Due to the increased demand for thyroid hormone during pregnancy, dietary iodine requirements are higher in pregnant women (28). Adequate iodine intake before and during pregnancy is vital to ensure enough iodine stores in this period, which is about 250 μg iodine daily (2). Iodine sources are fish, shellfish, iodized food, iodized salt, iodized drinking water or iodine supplements. Universal salt iodization is the most cost-effective way of providing iodine and it is used by more than 70% of households worldwide (30).

It is questionable whether a geographic area with previous studies demonstrating a moderate or severe iodine deficiency has criteria in itself to perform universal screening for thyroid dysfunction if iodine supplementation strategies are implemented. To the best of our knowledge, there are no studies with the aim of evaluating if empiric iodine supplementation could be an alternative to the universal screening for thyroid dysfunction. On the one hand, iodine fortification proved to be effective in improving cognitive performance and reducing the prevalence of neurological abnormalities, stillbirth and neonatal and infant mortality in areas of severe iodine deficiency (31, 32). Neurodevelopmental outcomes were improved in areas of mild to moderate deficiency (32). To note, the beneficial outcomes of iodine on offspring depends on the timing of supplementation, that ideally should start in preconception or at least up to early pregnancy, since the effects are lost if started after 10-20 weeks gestation (33). On the other hand, to guarantee the iodine supplementation of all women of reproductive age, its implementation would have to reach the entire population of that geographic area. However, a single route of iodine supplementation may not be ingested by everyone, with the risk of thyroid dysfunction remaining in some people. Moreover, the fortification of various foods may cause excess iodine intake. Although most individuals are tolerant of chronic excess iodine intake, some people, and particularly the foetus and

TPOAb-positive women, can develop hypothyroidism in case of inability to escape from the Wolff-Chaikoff effect (2). Furthermore, studies showed an increased prevalence of thyrotoxicosis, another thyroid dysfunction, in populations exposed to excess iodine by fortified drinking water, including in newborns (34). In Portugal, it is not uncommon for physicians to evaluate TSH levels before starting iodine supplementation.

Cost-effectiveness: The cost-effectiveness of the screening is an important issue. Universal screening is defended as cost-effective in preconception by Maheshwari et al. and in pregnancy by Taylor et al. and Velasco and Taylor (14, 16, 18), even if we assume that only overt thyroid dysfunction cause adverse outcomes (18). Springer et al., however, report the lack of evidence of the cost-effectiveness of the screening in pregnancy (17).

Currently, there are very few cost-effectiveness studies in this area and it is unclear whether universal screening for thyroid dysfunction is cost-effective in either phase (14). A cost-effectiveness analysis performed in USA revealed that universal screening is cost-effective in pregnancy as compared to no screening (a gain of 589.3 QALYs for 100,000 women) (35). Later, another evaluation in USA not only reinforced previous results, but also defended that universal screening was cost-effective as compared to selective screening (36). An analysis conducted in Spain concluded that universal screening in the first trimester was a cost-effective strategy as compared to no screening (incremental cost-effectiveness ratio of 374 euros per QALY). Furthermore, universal screening allowed the treatment of overt and subclinical cases not detected in the selective method (37). Nevertheless, interpretation of these studies has to be cautious since their statistical models were based on data from other populations.

Practical recommendations: Considering the points discussed above, the arguments in favour and against universal screening implementation is summarized in Table 2.

Even though selective screening is generally practiced, as recommended by the 2017 ATA guidelines, available data allows us to recommend universal screening for thyroid dysfunction in early pregnancy (weak recommendation, low-quality evidence).

To address the problem that the grade of our recommendation on pregnant women screening is not robust, the most logical approach may be an individualized analysis by each country on the most appropriate screening method (universal versus selective), considering their characteristics. This assessment should consider the prevalence of fertile women with at least one of the ATA criteria and the prevalence of thyroid dysfunction in pregnant women. Additionally, cost-effectiveness studies should be conducted. Beyond the analysis performed by Spain regarding pregnancy period (25, 37), some authors discussed and advocated a universal screening in their country, namely China in the preconception period and Poland in pregnant women. However, they did not evaluate the health gains and costs associated with the institution of universal screening, as far as we know (38, 39).

Perspective on a country: We intended to assess the situation of Portugal. To the best of our knowledge, there are no multicentre studies on thyroid dysfunction or thyroid autoimmunity in Portuguese women during preconception or pregnancy. One study in 1673 people aged between 18 and 79 years old in five regions of Portugal detected a TSH level higher than the upper limit of normal reference in 8.79% (52% women) and a TSH level lower than the lower limit of normal in 1.2% (60% women) (40).

Table 2: Summary of arguments in favour and against universal screening for thyroid dysfunction in preconception or early pregnancy

In favour	Against
- Common disorder in fertile women (public health problem); - Selective screening needs timely and careful evaluation of the criteria and even then, a significant number of cases are missed; - Easy and low-cost diagnosis; - Safe (no harm of low dose of levothyroxine), easy and inexpensive treatment; - Potential of the treatment in the prevention of negative outcomes; - It can be performed in the preconception visit or in the first pregnancy visit, not overburdening the health care system; - TSH assessment before iodine supplementation to prevent thyrotoxicosis is not uncommon and is actually a screening for thyroid dysfunction.	- Absence of population and trimester cut-off levels of TSH in many countries; - Insufficient high-quality data on effectiveness of treatment in reducing adverse outcomes of subclinical hypothyroidism or positive TPOAb-positive women with TSH ≥ 2.5 mIU/L; - Dubious benefit in areas with iodine supplementation that covers the entire population; - Timely screening since most beneficial effects of treatment occur up to the middle of the first trimester of pregnancy.

Recently, a nationwide cross-sectional study with a subsample of 486 randomly selected participants (57.8% women) from 4095 adults showed a prevalence of 4.9% of overt hypothyroidism, 2.5% of overt hyperthyroidism and 11.9% of TPOAb positivity (41).

When we aim to apply ATA selective criteria on reproductive age women in Portugal, there are no reliable data to compare the costs between universal and selective screenings. Some of these criteria refer to very specific and low prevalence conditions, which is not possible to evaluate.

If we consider only the recommendation for screening of pregnant women over 30 years old (possibly the most common ATA criterion in Portugal), we estimated a cost of 279,995 euros in selective screening and more 148,580 euros in universal screening in 2017 in Portugal, according to the data of National Statistical Institute and the last table of the National Health System (42, 43). However, we cannot estimate to gain health to perceive if it would favour a universal screening.

Regarding iodine deficiency in Europe, the World Health Organization (WHO) issued a report in 2007. It highlighted pregnant women and children as the groups at greatest risk and recommended the monitoring of thyroid function during pregnancy, especially in countries where such data were missing, namely Portugal and Bosnia-Herzegovina (44). In the following years, some research studies in Portugal were conducted, mostly in hospitals and maternity centers. A countrywide study evaluated 3631 pregnant women followed in 17 Portuguese maternity hospitals and revealed a median urinary iodine concentration (UIC) of 82.5 μg/L (84.9 μg/L in Continental Portugal, 69.5 μg/L in Madeira and 50.0 μg/L in Azores) (28). Portugal was then considered as a mild gestational iodine deficiency area, as some European countries (45). However, prevalence of moderate to severe iodine deficiency in pregnancy was 25.5% (23.7% in Continental Portugal, 33.7% in Madeira and 50.0% in the Azores), which is not negligible (28). Moreover, only 15.7% of pregnant women had adequate values (> 150 μg/L). National studies led to the official recommendation of universal iodine supplementation of women without known thyroid disease during preconception, pregnancy and lactation, in the form of potassium iodide (46). Although there is an ATA criterion based on geographical areas of iodine deficiency and Portugal was considered a mild gestational iodine deficiency area, this criterion no longer seems to apply to Portugal since universal iodine supplementation has already been instituted. It would be interesting to confirm this presumption, because no further studies regarding iodine status were performed since Limbert et al (28).

Currently, Portugal has not yet population- and trimester- specific TSH reference values. However, a multi-center study in pregnant women is being planned.

The summary of internal strengths and weaknesses and external opportunities and threats (i.e., SWOT analyses) of this review are presented in Table 3.

Conclusion

According to the articles reviewed, considering the potential in reducing adverse outcomes and the irrelevant risk of low dose of levothyroxine associated with the feasible, easy and low cost of TSH assessment, we recommend universal screening for thyroid dysfunction in early pregnancy, which is a distinct point of view from 2017 ATA guidelines (weak recommendation, low-quality evidence). Due to insufficient evidence, it is not possible to make a formal recommendation for preconception.

Table 3: SWOT analysis

Strengths	Weaknesses
• The first evidence-based review on the best screening method for thyroid dysfunction during preconception and pregnancy since the publication of ATA guidelines; • Extensive selection of publications, with restricted criteria; exclusion of pregnant women with conditions that may lead to thyroid dysfunction; • Topic of great interest, prevalence and impact on the population health, so concrete response is needed; • Analysis of the major key points of discussion of both screening methods; Practical recommendations and perspective of a country.	• Problem of taking robust conclusions due to weak or lacking evidence; • TSH assessment without TPOAb do not differ the need of treatment in some cases of subclinical hypothyroidism.
Opportunities	**Threats**
Given there is no strong recommendation force for the decision on the best screening method, this study highlights the need for an individualized evaluation and future randomized controlled trials to reach a high level of evidence data to guide clinical practice.	• Limited number of studies and their lack of high-quality data do not allow to draw firm conclusions. Uncertainty of TSH reference range in pregnancy and if levothyroxine treatment can improve outcomes.

Notably, we suggest an individualized analysis by each country on the most appropriate screening method (universal versus selective) considering their individual characteristics. This assessment should consider the prevalence of fertile women with at least one of the ATA criteria (namely the iodine status) and cost-effectiveness studies should be conducted. In a primary analysis, current national data is sparse to establish the best screening method in Portugal. However, if TSH may prove to be assessed prior starting iodine supplementation (which is universally recommended), the recommendation for universal screening for thyroid dysfunction should be considered.

As the controversy remains, this review highlights the need for future randomized controlled studies in the topic to reach high level of evidence data to guide clinical practice.

Conflict of Interests

Authors have no conflict of interests.

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References

1. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012; 97: 2543-65.
2. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27: 315-89.
3. Martinez M, Soldevila B, Lucas A, Velasco I, Vila L, Puig-Domingo M. Hypothyroidism during pregnancy and its association to perinatal and obstetric morbidity: a review. Endocrinol Diabetes Nutr 2018; 65: 107-13.
4. Stagnaro-Green A. Clinical guidelines: Thyroid and pregnancy-time for universal screening? Nat Rev Endocrinol 2017; 13: 192-4.
5. Koehler VF, Auernhammer CJ, Spitzweg C. [The Thyroid and Pregnancy]. Dtsch Med Wochenschr 2019; 144: 1681-5.
6. Sitoris G, Veltri F, Kleynen P, Cogan A, Belhomme J, Rozenberg S, et al. The Impact of Thyroid Disorders on Clinical Pregnancy Outcomes in a Real-World Study Setting. Thyroid 2020; 30: 106-15.
7. Lee SY, Cabral HJ, Aschengrau A, Pearce EN. Associations Between Maternal Thyroid Function in Pregnancy and Obstetric and Perinatal Outcomes. J Clin Endocrinol Metab 2020; 105: e2015-e23
8. Cigrovski Berkovic M, Herman Mahecic D, Marinkovic Radosevic J, Strinovic Moric M, Bilic-Curcic I. Hypothyroidism and pregnancy: still a controversial issue. Gynecol Endocrinol 2020; 36: 776-780.
9. Poppe K, Velkeniers B, Glinoer D. The role of thyroid autoimmunity in fertility and pregnancy. Nat Clin Pract Endocrinol Metab 2008; 4: 394-405.
10. Liu H, Shan Z, Li C, Mao J, Xie X, Wang W et al. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid 2014; 24: 1642-9.
11. Kalra S, Baruah MP, Unnikrishnan AG. Hypothyroidism in pregnancy: From unanswered questions to questionable answers. Indian J Endocrinol Metab 2013; 17: 200-2.
12. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006; 91: 2587-91.
13. Korevaar TI. Evidence-Based Tightrope Walking: The 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017; 27: 309-11.
14. Maheshwari A, Bhide P, Pundir J, Bhattacharya S. Routine serum thyroid-stimulating hormone testing-optimizing pre-conception health or generating toxic knowledge? Hum Reprod 2017; 32: 1779-85.
15. Kalra B, Gupta Y, Kalra S. Preconception management of thyroid disorders. JPMA The Journal of the Pakistan Medical Association 2017; 67: 645-7.
16. Velasco I, Taylor P. Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies. Eur J Endocrinol 2018; 178: D1-D12.
17. Springer D, Jiskra J, Limanova Z, Zima T, Potlukova E. Thyroid in pregnancy: From physiology to screening. Crit Rev Clin Lab Sci 2017; 54: 102-16.
18. Taylor PN, Zouras S, Min T, Nagarajah K, Lazarus JH, Okosieme O. Thyroid screening in early pregnancy: pros and cons. Frontiers in endocrinology 2018; 9: 626.
19. Akram FH, Johansson B, Mollerstrom G, Landgren BM, Stavreus-Evers A, Skjoldebrand-Sparre L. Incidence of Subclinical Hypothyroidism and Hypothyroidism in Early Pregnancy. J Womens Health (Larchmt) 2017; 26: 1231-5.
20. Pop VJ, Broeren MA, Wiersinga WM, Stagnaro-Green A. Thyroid disease symptoms during early pregnancy do not identify women with thyroid hypofunction that should be treated. Clin Endocrinol (Oxf) 2017; 87: 838-43.
21. Rosario PW. Selective screening for thyroid dysfunction in pregnant women: How often do low-risk

women cease to be treated following the new guidelines of the American Thyroid Association? Arch Endocrinol Metab 2018; 62: 641-3.
22. Akter F, Kamrul-Hasan A, Ahmed E, Selim S, Aalpona F, Emran M, et al. Thyroid Dysfunction and Autoimmunity in First Trimester of Pregnancy, Single Center Experience in Bangladesh. Mymensingh medical journal: MMJ 2018; 27: 603-9.
23. Sitoris G, Veltri F, Kleynen P, Belhomme J, Rozenberg S, Poppe K. Screening for thyroid dysfunction in pregnancy with targeted high-risk case finding: can it be improved? J Clin Endocrinol Metab 2019; 104: 2346-54
24. Koren R, Wiener Y, Or K, Benbassat CA, Koren S. Thyroid Disease in Pregnancy: A Clinical Survey among Endocrinologists, Gynecologists, and Obstetricians in Israel. Isr Med Assoc J 2018; 20: 167-71.
25. Vila L, Velasco I, Gonzalez S, Morales F, Sanchez E, Lailla JM, et al. Detection of thyroid dysfunction in pregnant women: universal screening is justified. Endocrinol Nutr 2012; 59: 547-60.
26. Wilson JMG, Jungner G, Organization WH. Principles and practice of screening for disease. Bol Oficina Sanit Panam 1968; 65: 281-393.
27. Vanderpump MP. The epidemiology of thyroid disease. British medical bulletin 2011; 99: 39-51.
28. Limbert E, Prazeres S, Sao Pedro M, Madureira D, Miranda A, Ribeiro M et al. Iodine intake in Portuguese pregnant women: results of a countrywide study. Eur J Endocrinol 2010; 163: 631-5.
29. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 2015; 3: 286-95.
30. Pearce EN, Andersson M, Zimmermann MB. Global iodine nutrition: Where do we stand in 2013? Thyroid 2013; 23: 523-8.
31. DeLong GR, Leslie PW, Wang SH, Jiang XM, Zhang ML, Rakeman M, et al. Effect on infant mortality of iodination of irrigation water in a severely iodine-deficient area of China. Lancet 1997; 350: 771-3.
32. O'Donnell KJ, Rakeman MA, Zhi-Hong D, Xue-Yi C, Mei ZY, DeLong N, et al. Effects of iodine supplementation during pregnancy on child growth and development at school age. Dev Med Child Neurol 2002; 44: 76-81.
33. Vandevijvere S, Amsalkhir S, Mourri AB, Van Oyen H, Moreno-Reyes R. Iodine deficiency among Belgian pregnant women not fully corrected by iodine-containing multivitamins: a national cross-sectional survey. Br J Nutr 2013; 109: 2276-84.
34. Chen W, Sang Z, Tan L, Zhang S, Dong F, Chu Z, et al. Neonatal thyroid function born to mothers living with long-term excessive iodine intake from drinking water. Clin Endocrinol (Oxf) 2015; 83: 399-404.
35. Thung SF, Funai EF, Grobman WA. The cost-effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am J Obstet Gynecol 2009; 200: 267 e1-7.
36. Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. J Clin Endocrinol Metab 2012; 97: 1536-46.
37. Donnay Candil S, Balsa Barro JA, Alvarez Hernandez J, Crespo Palomo C, Perez-Alcantara F, Polanco Sanchez C. [Cost-effectiveness analysis of universal screening for thyroid disease in pregnant women in Spain]. Endocrinol Nutr 2015; 62: 322-30.
38. Zhou Q, Acharya G, Zhang S, Wang Q, Shen H, Li X. A new perspective on universal preconception care in China. Acta Obstet Gynecol Scand 2016; 95: 377-81.
39. Hubalewska-Dydejczyk A, Trofimiuk-Müldner M. The development of guidelines for management of thyroid diseases in pregnancy – current status. Thyroid Res 2015; 8: A11.
40. Ramos T, Mariano C, Bourbon M. [Analysis of thyroid function in the Portuguese adult population] Boletim Epidemiológico Observações 2017; 6: 13-6.
41. Raposo L, Martins S, Ferreira D, Guimarães JT, Santos AC. Metabolic Syndrome, Thyroid Function and Autoimmunity-The PORMETS Study. Endocr Metab Immune Disord Drug Targets 2019; 19: 75-83.
42. Portuguese Institute of Statistics (INE). [Health Statistics: 2017]. Lisboa: INE, 2019. Available at: https://www.ine.pt/xurl/pub/320460040.
43. Central Administration of the Health System (ACSS). [Report on diagnostic tests and therapies, 2017] .Available at: http://www.acss.min-saude.pt/2016/10/03/tabelas-meios-complementares-de-diagnostico-e-terapeutica./
44. Andersson M, De Benoist B, Darnton-Hill I, Delange F. Iodine deficiency in Europe: a continuing public health problem: World Health Organization Geneva, 2007.
45. Trumpff C, De Schepper J, Tafforeau J, Van Oyen H, Vanderfaeillie J, Vandevijvere S. Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: a review. J Trace Elem Med Biol 2013; 27: 174-83.
46. Portuguese Directorate-General of Health (DGS). Iodine intake in women in preconception, pregnancy and breastfeeding; national guideline 011/2013.

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