A 2018 Italian and Romanian Survey on Subclinical Hypothyroidism in Pregnancy

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Keywords

Thyroid · Hypothyroidism · Autoimmunity · Pregnancy · Survey · Guidelines

Abstract

Objectives: Pregnancy induces changes in thyroid function, and thyroid dysfunction during gestation is associated with adverse outcomes. We examined the management of subclinical hypothyroidism and chronic autoimmune thyroiditis in pregnancy among Italian and Romanian endocrinologists.

Methods: Members of the Associazione Medici Endocrinologi (AME) and Romanian Society of Endocrinology (RSE) were invited to participate in a web-based survey investigating the topic. **Results:** A total of 902 individuals participated in the survey, 759 of whom completed all sections. Among the respondents, 85.1% were aware of the 2017 American Thyroid Association guidelines about thyroid disease and pregnancy, and 82.9% declared that thyroid-stimulating hormone (TSH) screening at the beginning of pregnancy should be warranted. In a patient negative for peroxidase antibodies, 53.6% considered 2.5 mIU/L and 26.2% considered 4.0 mIU/L as the upper normal limit of TSH, and 50% would treat

a patient with TSH 3.5 mIU/L with levothyroxine. About 20% did not suggest iodine supplementation. Isolated hypothyroxinemia detected in the first trimester would be treated by 40.8%. In patients undergoing ovarian stimulation, a TSH <2.5 mIU/L would be targeted by 70%. **Conclusions:** Respondents globally appeared well informed about the management of thyroid autoimmunity and subclinical hypothyroidism in pregnancy. A more aggressive attitude in implementing iodine supplementation would be desirable. Most endocrinologists were convinced about an evident association between mild thyroid impairment and adverse outcomes in pregnancy, thus using a TSH value of 2.5 mIU/L as the threshold for diagnosing hypothyroidism and starting levothyroxine in pregnant women.

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Introduction

An increasing number of studies focusing on thyroid disease and pregnancy have been published over the last decades. Such interest has been driven by at least 2 factors: the relevant number of women suffering from thyroid dis-

ease in childbearing age, and the evidence of adverse events especially associated with overt thyroid disease. Among thyroid diseases, thyroid autoimmunity (TAI) and subclinical hypothyroidism (SCH) are by far the most frequent, involving at least 10% of the female population [1, 2]. However, consistent data have been published only about the association between overt hypothyroidism and miscarriage or a reduced intelligence quotient in the offspring; conversely, data about detrimental effects associated with subclinical dysfunction are conflicting [3, 4]. Over the years, scientific societies of endocrinologists in the USA and Europe have released guidelines to provide evidence-based medicine suggestions for clinical practice [5–7]. In 2017, the American Thyroid Association (ATA) published updated guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum [8]. The present survey was aimed to investigate how these guidelines were perceived by Italian and Romanian endocrinologists, particularly in reference to SCH and TAI, and to what extent they changed endocrinologists' clinical practice compared to the past.

Materials and Methods

A web-based survey was constructed with Lime-Survey, an open-access platform that provides various question templates. The questionnaire included 33 questions (online suppl. material; see www.karger.com/doi/10.1159/000490944 for all online suppl. material). A total of 2,060 Associazione Medici Endocrinologi (AME) and 453 Romanian Society of Endocrinology (RSE) members were sent an initial e-mail including an electronic link to the questionnaire, followed by weekly reminders from the AME secretariat, from February to March 2018. Survey responses were anonymously collected and electronically stored by the survey service, where they were accessible by password. The survey service automatically blocked repeat submissions from the same IP address.

Statistical Analysis

Summary statistics were prepared for responses to each question. We considered only those questionnaires that were fully completed as valid for statistical evaluation. A χ^2 test was used to evaluate the questionnaire response rates. Data were analyzed using IBM SPSS statistics version 19 software (SPSS, Chicago, IL, USA). Ethical approval or patient consent were not applicable for this kind of investigation.

Results

A total of 745 individuals from Italy (36.2% of AME members) and 157 from Romania (34.6% of RSE members) participated in the survey. Of these, 637 (30.9%)

from Italy and 122 (26.9%) from Romania completed all the sections. Thus, 759 complete questionnaires were finally considered for statistical evaluation.

Among the respondents, females accounted for 64.2%. The age distribution was as follows: 3%, <30 years; 27.3%, 31–40 years; 22%, 41–50 years; 27.3%, 51–60 years; 20.4%, >60 years. Of the respondents, 95.4% specialized in endocrinology, 3.8% in internal medicine, 0.4% in nuclear medicine, and 0.4% in pediatric endocrinology. Places of employment included referral hospitals (37.8%), private practices (36.4%), district hospitals (14.5%), and university hospitals (11.3%). Characteristics were similar between respondents and the whole cohort of AME and RSE members. Of the participants, 7.5% were mainly involved in diabetes, 54.9% in thyroid disease, and 37.6% in both (thyroid vs. others, $p < 0.01$). A total of 60.7% reported performing thyroid ultrasound on a regular basis ($p < 0.01$), and 85.1% were aware of the 2017 ATA guidelines about thyroid disease and pregnancy ($p < 0.01$).

About two-thirds advise patients with thyroid dysfunction in writing to consult an endocrinologist when pregnancy occurs, while one-third do so orally ($p < 0.01$). More than 80% declared that screening for thyroid dysfunction by thyroid-stimulating hormone (TSH) at the beginning of pregnancy should be warranted ($p < 0.01$), and 60.5% believed that randomized clinical trials demonstrated a detrimental effect on intelligence quotients of babies from mothers with untreated SCH or isolated hypothyroxinemia (IH; $p < 0.01$). Respondents reported that in one-third of cases gynecologists follow a standardized protocol for the diagnosis of thyroid disease, whereas in two-thirds of cases the request for a thyroid function test is left to individual initiative ($p < 0.01$). More than 80% reported that the number of endocrine referrals for thyroid disease in pregnancy is increased (slightly or considerably) compared to the past ($p < 0.01$).

Iodine supplementation should always be implemented according to two-thirds of the respondents ($p < 0.01$), and about 50% suggest iodine supplementation also for patients with hypothyroidism already on replacement therapy ($p = \text{ns}$). Physicians equally use multivitamin pills containing iodine, iodized salt, or a pill containing iodine alone ($p = \text{ns}$). Urinary iodine excretion would never be requested by half (with the remaining requesting it in case of elevated TSH and/or low FT4), but for a third of endocrinologists this assay is not available (no urinary iodine vs. other options, $p < 0.01$).

In a pregnant patient negative for TPOAb, about half of respondents considered 2.5 mIU/L the normal upper limit of TSH (2.5 mIU/L vs. other TSH levels, $p < 0.01$;

Fig. 1. Upper limit of TSH considered as normal in a pregnant patient negative for TPOAb.

Fig. 2. Requested test for a pregnant woman in the first trimester with a TSH level of 3.8 mIU/L.

Fig. 3. Management of a hypothyroid (postsurgical or autoimmune) patient with a prepregnancy TSH level of 2.5 mIU/L.

Fig. 4. Targeted TSH concentration in a pregnant patient on LT4 treatment for hypothyroidism.

Fig. 5. Rates of physicians who would treat IH in the first and in the third trimester of pregnancy.

Fig. 1). To assess thyroid function, nearly half of the physicians would ask for FT4 in addition to TSH, and a little more than 10% for thyroid antibodies (FT4 vs. other options, $p < 0.01$). For a pregnant patient with a first-trimester TSH level of 3.8 mIU/L, the majority would ask for TPOAb + TgAb (TPOAb + TgAb vs. others, $p < 0.01$; Fig. 2).

Thyroid ultrasound would always be used by two-thirds of the respondents (always vs. other specific conditions, $p < 0.01$). In a pregnant patient in the first trimester with TSH 2.5 mIU/L and positive TPOAb, about 70%

would simply monitor TSH, about 20% would treat with levothyroxine (LT4), and more than 5% would suggest selenium supplementation (TSH monitoring vs. others, $p < 0.01$).

When the prepregnancy TSH level is 2.5 mIU/L, more than 50% would increase the LT4 dosage by 30% both in postsurgical and autoimmune hypothyroidism ($p = ns$; Fig. 3). When the hypothyroid pregnant patient is on replacement with LT4, two-thirds would like to keep TSH < 2.5 mIU/L ($p < 0.01$; Fig. 4).

The occurrence of first-trimester TSH of 3.5 mIU/L (negative TPOAb, and normal ultrasound) would prompt LT4 treatment in half of respondents ($p = ns$). IH would be treated with LT4 by about 40% in the first trimester, and by 17.1% in the third trimester ($p < 0.01$; Fig. 5).

In a patient on LT4 undergoing assisted reproduction technology (ART), about one-third would pursue an ovarian prestimulation TSH < 1.5 mIU/L, and two-thirds < 2.5 mIU/L ($p < 0.01$; Fig. 6). In a patient with TAI (without LT4 treatment), LT4 was suggested when TSH is > 2.5 mIU/L by the majority (70.1%; TSH > 2.5 mIU/L vs. other cut-offs, $p < 0.01$). TSH would be checked by the relative majority (45.2%) during ovarian stimulation (during ovarian stimulation vs. other timings, $p < 0.01$). Of the respondents, 97.2% would not suggest steroid treatment in women with TAI undergoing ART ($p < 0.01$).

During pregnancy, TSH would be monitored twice during the first trimester and once during the second and the third trimesters by about 40%, monthly by 50%, and once each trimester by less than 10% (monthly vs. others, $p < 0.05$). Overall, no relevant differences could be detected between Italian and Romanian endocrinologists.

Fig. 6. Preferred TSH concentration in a patient undergoing ovarian stimulation.

Discussion

The present survey depicts Italian and Romanian endocrinologists' attitude in diagnosing and managing TAI and SCH in relation to pregnancy, following the publication of the ATA guidelines in 2017 [8]. More than half of our respondents were mainly involved in thyroid disease and the overwhelming majority were aware of the ATA guidelines, revealing a great interest in this field and the importance of such guidelines.

A huge number of physicians were in favor of universal screening for thyroid dysfunction in pregnancy, and the majority were convinced that untreated SCH or IH lead to a reduced intelligence quotient (IQ) in the offspring. A previous survey among European Thyroid Association (ETA) members revealed that 42% of respondents screened all pregnant women and 43% adopted a case-finding approach; in another survey, 75% of Iranian endocrinologists opted for targeted screening, whilst universal screening was supported by 57% in Israel and by 43% in Latin America [9–12]. Two large-scale trials failed to demonstrate any benefit of LT4 on cognitive outcomes, and a recent study found a similar proportion of children with an IQ <85 from women with normal and suboptimal gestational thyroid function [13–15]. Although the official stance of international endocrine societies was neither “for” nor “against” universal screening, it is clear that the majority of endocrinologists in the present survey supported universal screening, also due to overestimating of the benefits derived from treating SCH [5–8]. The collected responses suggest that an involuntary screening is progressively taking place, as endocrinologists reported

that the number of consultations for thyroid dysfunction is greater than in the past.

Iodine deficiency still represents a health issue both in the USA and Europe [16–18]. A systematic review and meta-analysis showed that iodine supplementation exerts some benefits in children's cognitive function [19]. The importance of an adequate iodine status during early gestation and the risk that iodine deficiency can pose to the developing infant has been clearly shown in the Avon Longitudinal Study of Parents and Children (ALSPAC) study [20]. Then, despite mild-to-moderate iodine deficiency being more marked in Italy than in Romania, a remarkable number of endocrinologists ignored the ATA recommendation to supplement women, preferably even before pregnancy, by the ingestion of approximately 250 µg of iodine daily; by contrast, half suggested supplementation in LT4-replaced patients, which is considered unnecessary [21, 22].

Half of respondents considered 2.5 mIU/L as the upper limit of the normal reference range for a pregnant woman in the first trimester (TPOAb negative), whilst a quarter considered 4.0 mIU/L to be the upper limit of normal. The ATA suggestion to elevate the upper limit of TSH from 2.5 to 4.0 mIU/L is probably one of the more significant changes introduced [5, 8]. Such change derived from studies published after 2011 (the year of publication of the previous guidelines), indicates, especially in the population outside the USA, only a modest reduction in the TSH reference limit [23–25]. To assess thyroid function, TSH was often obtained in conjunction with FT4; for a patient with TSH around the upper limit, both TPOAb and TgAb would be requested by the majority,

although ATA guidelines recommend assessment of TPOAb only. Of note, a study from Belgium in women seeking fertility treatment showed that those with isolated TgAb positivity had a significantly higher serum TSH than women without TAI [26]. Response rates clearly indicate that assessing antibody status is considered more important than monitoring TSH, although these 2 options are not mutually exclusive in clinical practice.

For a first-trimester euthyroid patient (TSH 2.5 mIU/L) suffering from TAI, the vast majority would simply monitor TSH. The active surveillance of TSH during pregnancy is justified by the evidence that about 20% of euthyroid women with TAI show TSH values >4.0 mIU/L throughout gestation [27, 28]. Whether or not LT4 treatment (suggested by about 20% of respondents) might decrease adverse events such as pregnancy loss or preterm delivery is still a matter of debate, but a small amount of LT4 (25–50 µg daily) may be considered.

Once pregnant, hypothyroid women on LT4 usually require an increase of their daily amount. The magnitude of increase depends on the cause of hypothyroidism (postsurgical or autoimmune) and the prepregnancy TSH concentration, but it usually comprises between 30 and 50% [29–31]. Our cohort of endocrinologists appears quite prudent in carrying out an LT4 increase, as more than 40% opted simply for TSH monitoring. This attitude was similar to that observed in another survey among ETA members. Also in that survey, a similar rate of respondents preferred to monitor TSH before increasing the LT4 daily amount, and aimed to keep TSH <2.5 mIU/L during the first trimester [9].

As further proof that a consistent number of endocrinologists still consider 2.5 mIU/L as the upper limit of TSH, 40% would treat a first-trimester woman who is negative for thyroid antibodies with a TSH level of 3.5 mIU/L. A similar attitude was previously demonstrated by other surveys published between 2012 and 2018, all showing that keeping TSH <2.5 mIU/L is a common attitude, especially when TPOAb are positive [10–12]. Since the publication of previous ATA guidelines in 2011, several studies have shown that the number of women defined as hypothyroid, and consequently treated, remarkably increased when considering 2.5 mIU/L as the cut-off value [32–34]. It should be noted that many have patently misunderstood the suggestions released by the 2011 ATA guidelines, which suggested LT4 with TSH >2.5 mIU/L and positive TPOAb, but also stated that there was insufficient evidence to recommend for or against universal LT4 treatment in antibody-negative women [5].

Two large-scale trials failed to demonstrate a benefit in treating hypothyroxinemic women, but a large population-based prospective cohort study demonstrated that both low and high maternal FT4 concentrations were associated with lower child IQ and lower grey matter and cortex volume [9, 14, 35]. The 2014 ETA guidelines stated that LT4 therapy may be considered when hypothyroxinemia is detected in the first trimester (but not in the second and the third trimesters) [7]; the ATA guidelines suggest that this condition should not be routinely treated [8]. The inclination to treat hypothyroxinemic women is patent in our cohort of endocrinologists, who considered LT4 in 40% of cases in the first trimester. Of note, a similar rate (38%) was obtained by European endocrinologists, confirming that this condition is far from being properly characterized [9].

Another important issue investigated among our cohort of endocrinologists involved the management of a woman undergoing ART. During the procedure, a TSH elevation is observed in hypothyroid patients on LT4, particularly 1 week after hCG administration, and 84% of women on replacement treatment and a prefertilization TSH <2.5 mIU/L require an LT4 increase [36, 37]. In such cases it seems reasonable to obtain a TSH concentration <2.5 mIU/L through this approach, and possibly <1.5 mIU/L, and to start treatment with LT4 in women positive for thyroid antibodies with a prestimulation TSH >2.5 mIU/L [38]. As controlled ovarian stimulation negatively alters thyroid parameters when TPOAb are positive, respondents would check TSH levels in hypothyroid women on LT4 (with about half pointing out that the correct timing is during ovarian stimulation). In fact, a blunted TSH and T4 response to hCG has been observed in spontaneously pregnant women with TAI, and the risk of an abnormal TSH elevation is remarkable in those undergoing ovarian stimulation [36, 37, 39]. In accordance with current guidelines, the overwhelming majority did not recommend glucocorticoid therapy for TPOAb-positive euthyroid women undergoing ART. In the end, once the hypothyroid woman on LT4 is pregnant, TSH monitoring throughout gestation looks likely to be adequate anyway.

As a conclusion, the Italian and European endocrinologists who answered the questionnaire appeared to be generally well informed about the management of TAI and SCH in relation to pregnancy. At least 3 points need to be highlighted: (1) a more aggressive attitude in implementing iodine supplementation would be desirable, considering that iodine deficiency is still an issue, also in developed countries; (2) IH is considered worthy of treat-

ment by a remarkable number of endocrinologists in spite of inconsistent evidence; (3) the local reference range was available only for a minority of endocrinologists, about 25% adopted 4.0 mIU/L as the upper limit of TSH, but more than 50% used 2.5 mIU/L as the threshold for diagnosing and treating SCH. Clearly, the idea that even mild thyroid impairment is associated with adverse events is stronger than the available evidence, and still drives our cohort of endocrinologists to treat patients with LT4 who do not really need to be treated. One could speculate that the previous evidence supporting an upper

limit of TSH around 2.5 mIU/L had a remarkable impact on the endocrinologists and continues to influence their clinical attitudes. In this view, the present results deserve consideration from the endocrine scientific societies in providing their members with updated evidence that could support a better quality of patient care.

Disclosure Statement

The authors have nothing to disclose.

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