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CLINICAL STUDY

Treatment and screening of hypothyroidism in pregnancy: results of a European survey

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Abstract

Background: Maternal hypothyroidism in pregnancy is associated with several adverse outcomes. The Endocrine Society Guidelines for the management of thyroid diseases in pregnancy were published in 2007; however, impact of the guidelines in routine clinical practice is unknown. Therefore, we have carried out a survey of members of the European Thyroid Association (ETA) to study current practices relating to the management of hypothyroidism in pregnancy.

Subjects and methods: In December 2010, we emailed an electronic questionnaire survey based on clinical case scenarios to 605 members of the ETA. Responses from 190 clinician members (from 28 European countries) were analyzed.

Results: For a pregnant woman with newly diagnosed overt hypothyroidism, most responders initiated a full dose of L-thyroxine (L-T_4). For a woman with hypothyroidism planning pregnancy, 50% recommended increasing the dose of L-T_4 as soon as pregnancy is confirmed, whilst 43% favored testing thyroid function before adjusting the dose. Responders used diverse combinations of tests to monitor the dose of L-T_4. The target of thyroid function tests that responders aimed to achieve with L-T_4 was also inconsistent. Forty-two percent responders or their institutions screened all pregnant women for thyroid dysfunction, 43% performed targeted screening of only the high-risk group, whilst 17% did not carry out systemic screening. Timing of the screening, tests used, and criteria for starting treatment and monitoring were variable.

Conclusions: There is wide variation in the clinical practice relating to the treatment and screening of hypothyroidism during pregnancy in Europe.

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Introduction

Both overt and subclinical maternal thyroid hormone deficiencies are common in pregnancy, and are associated with several adverse outcomes, including miscarriage, premature birth, gestational hypertension, placental abruption, fetal growth retardation, and impaired neuropsychological development of the offspring (1). Whilst it is generally accepted that optimal treatment of maternal hypothyroidism is important to achieve a successful pregnancy outcome, how to detect and treat maternal hypothyroidism in pregnancy remains a matter of controversy (2, 3). The Endocrine Society Guidelines for the management of thyroid diseases, including hypothyroidism, in pregnancy were published in 2007 (4). Since the publication of the guidelines, many new studies – including randomized controlled trials (5, 6) – have provided further evidence-base for clinical practice in the field and prompted development of the more recent guidelines from the American Thyroid Association (ATA) (7). However, it remains uncertain as to what extent clinicians follow these guidelines in their routine clinical practice. Therefore, we have carried out a survey of members of the European Thyroid Association (ETA) to study the prevalent current practices relating to the treatment and screening of hypothyroidism during pregnancy in Europe.

Subjects and methods

In December 2010, an electronic questionnaire survey was emailed to 605 members of the ETA. This was followed by a reminder email in January 2011. The survey was based on clinical case scenarios, and asked questions about the clinical practices related to the management of hypothyroidism and hyperthyroidism in

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pregnancy. Only results concerning the treatment and screening of hypothyroidism during pregnancy are presented in this report. Two authors (B Vaidya and K Poppe) prepared an initial draft of the survey questionnaire covering key contentious issues on the topic. The draft questionnaire was piloted amongst the co-authors. Following the pilot and feedback from all the co-authors, the questionnaire was revised and finalized for wider distribution. In total, there were 16 multiple choice questions on management of hypothyroidism and screening thyroid function in pregnancy. Responders were asked to select single (13 questions) or multiple (3 questions) answers. However, for most questions, they were also able to provide their own answer if it was not included in the questionnaire. A copy of the questionnaire is available on request from the authors.

All frequencies were adjusted on a 100% basis excluding the non-responders. Results are predominantly presented as percentages, rounded up to a whole number in the text and up to one decimal point in the tables.

Results

Characteristics of responders

We received 210 responses from 32 countries. Fourteen responders were not involved in the management of thyroid diseases in pregnancy. Six responders were from non-European countries (three USA, one China, one Australia, and one not specified), and were not included in the current analysis. Therefore, responses from 190 responders practicing in 28 European countries were analyzed. Although the ETA membership database does not distinguish clinician and basic science members, it is estimated that the responders in this survey represent over 50% of practicing clinician members of the association. The countries with more than ten responders included Italy ($n=28$), Poland ($n=18$), Denmark ($n=17$), UK ($n=14$), and Turkey ($n=12$). Most of the responders were endocrinologists (90%); the remaining included nuclear medicine specialists (4%), surgeons (4%), general practitioners (2%), and general internists (0.5%).

A majority of responders (78%) reported that endocrinologists managed hypothyroidism in pregnancy in their institutions. In the remaining of the responders' institutions, the condition was managed by endocrinologists and obstetricians jointly in a multidisciplinary clinic (18%), obstetricians (2%), nuclear medicine specialists (2%), or general practitioners (2%).

Treatment of hypothyroidism in pregnancy

Responders were asked what dose of L-thyroxine (T_4) they would start for a 24-year-old woman, who is 12 weeks pregnant and has just been diagnosed with overt primary hypothyroidism. Responders suggested variable regimes to initiate L-T_4 replacement for the woman, although most recommended starting on a full replacement dose, empirically or based on pregnancy adopted body weight (Table 1). However, 6% of responders recommended a small starting dose of L-T_4 (25–50 μg/daily).

Most responders perceived that overt hypothyroidism diagnosed in the late first trimester, despite adequate L-T_4 replacement, would result in subtle (59% responders) or clinically significant (30% responders) neuropsychological impairment of the offspring; only 9% of responders felt that there would be no consequences to the offspring. Although a majority of responders (75%) would not endorse abortion in such a situation, 18% would recommend abortion, and a further 7% would discuss the option of abortion.

There was inconsistency in responders' recommendations on how to adjust the dose of L-T_4 in a hypothyroid woman, who is planning pregnancy (Table 2). Although 50% of responders would recommend the woman to increase the dose of L-T_4 as soon as pregnancy is confirmed, 43% would first check thyroid function tests before adjusting the dose. Likewise, responders' recommendations to a hypothyroid woman, who is in the process of undergoing ovarian hyperstimulation before IVF, were also variable (Table 2).

Responders used 14 different combinations of tests to monitor the dose of L-T_4 in pregnancy (Table 3). Likewise, the target thyroid function test results that responders aim to achieve with L-T_4 in pregnancy was also inconsistent, although a majority of responders aim to keep TSH <2.5 mIU/l in the first trimester and <3 mIU/l in the later trimesters (Table 4).

Table 1 Starting dose of L-thyroxine (L-T_4) in a pregnant woman diagnosed with overt hypothyroidism (TSH 86 mIU/l) at 12 weeks gestation.

Starting dose of L-T_4	Responders *n* (%)
Start on a small dose (e.g. 25–50 μg daily)	10 (6.2)
Start on a full dose (e.g. 100–125 μg daily)	74 (45.7)
Start on a dose based on pregnancy adopted body weight	29 (17.9)
Start for a few days on a double dose (e.g. 200 μg daily), then a dose based on pregnancy adapted body weight	40 (24.7)
Start on a dose based on pre-treatment TSH level	5 (3.1)
Other[a]	2 (1.2)

[a]Include i.v. 500 μg L-T_4, followed by 100–125 μg orally ($n=1$); advise abortion ($n=1$).

Table 2 Responders' recommendations to a hypothyroid woman treated with L-T_4 (TSH 2.4 mU/l), who is planning pregnancy or in the process of undergoing ovarian hyperstimulation before IVF procedure.

Recommendations	Responders *n* (%)	
	Planning pregnancy	In the process of ovarian hyperstimulation
Increase L-T_4 dose by 30–50% as soon as pregnancy is confirmed	72 (44.4)	30 (18.6)
Increase L-T_4 dose by two tablets per week as soon as pregnancy is confirmed	9 (5.6)	–
Check thyroid function as soon as pregnancy is confirmed/hyperstimulation, and increase L-T_4 dose if necessary	70 (43.2)	92 (57.1)
Increase L-T_4 dose before pregnancy/hyperstimulation	11 (6.8)	39 (24.2)

Screening pregnant women for thyroid dysfunction

Whilst 42% of responders or their institutions screened all pregnant women for thyroid dysfunction, 43% performed targeted screening of only the high-risk group and 17% did not carry out systemic screening. Responders carrying out the targeted screening used diverse risk factors to classify the 'high-risk' group (Table 5).

Responders' timing of screening thyroid function in pregnancy was variable; 67% screened in a pre-pregnancy visit, 22% in the first antenatal visit, and 11% did not have specific timing. Likewise, tests used for screening were also highly inconsistent (Table 3). Responders were asked whether they would routinely repeat thyroid function tests during the pregnancy if the initial screening was normal; 16% would routinely repeat the tests in later pregnancy, 53% would repeat only in the presence of thyroid peroxidase antibodies (TPO-Ab) or specific features on thyroid ultrasonography, and 31% would not repeat.

Responders used varied criteria to start L-T_4 replacement following the screening: TSH above the trimester-specific reference range, 31%; TSH above the population reference range, 15%; TSH above 2.5 mIU/l, 51%; TSH above 5 mIU/l, 15%; free T_4 (FT_4) below the trimester-specific reference range, 21%; and other criteria, 9%. There was also inconsistency in responders' approach to various outcomes of screening thyroid function in pregnancy (Fig. 1). For example, 38% of the responders would treat isolated hypothyroxinemia; whist 48% would follow-up without treatment. Furthermore, responders' definition of isolated hypothyroxinemia was not consistent: normal TSH with FT_4/ total T_4 (TT_4) below the trimester-specific reference range, 43%; normal TSH with FT_4/TT_4 below the population reference range, 30%; normal TSH with FT_4/TT_4 below the 2.5th centile, 12%; normal TSH with FT_4/TT_4 below the 5th centile, 7%; normal TSH with FT_4/TT_4 below the 10th centile, 5%; and other definitions, 2%.

Table 3 Different tests responders use to monitor L-T_4 dose and to screen thyroid dysfunction in pregnancy.

Tests	Responders *n* (%)	
	Monitoring L-T_4 dose	Screening thyroid dysfunction
TSH	19 (11.7)	23 (15.4)
TSH, FT_4	69 (42.6)	16 (10.7)
TSH, FT_4, FT_3	47 (29)	3 (2)
TSH, FT_4, TT_3	3 (1.9)	1 (0.7)
TSH, FT_4, TPO-Ab	2 (1.2)	41 (27.5)
TSH, FT_4, FT_3, TPO-Ab	–	18 (12.1)
TSH, TPO-Ab	–	18 (12.1)
Other combinations of tests	22 (13.6)[a]	29 (19.5)[b]

FT_4, free thyroxine; FT_3, free triiodothyronine; TPO-Ab, thyroid peroxidase antibodies; TT_3, total T_3.
[a]Nine different combinations of tests (various combinations of TSH, FT_4, Total T_4, FT_3, TT_3, T_4-uptake, and TPO-Ab).
[b]Eighteen different combinations of tests (various combinations of TSH, FT_4, Total T_4, FT_3, TT_3, T_4-uptake, TPO-Ab, antithyroglobulin antibodies, thyrotropin receptor antibodies, ultrasonography, and urinary iodine).

Discussion

This survey has demonstrated wide variation in clinical practices relating to the treatment and screening of maternal hypothyroidism in pregnancy in Europe. The Endocrine Society Guidelines (4) had been published for a few years at the time of the survey. There was a high degree of consistency between the guidelines and some aspects of the responders' clinical practice, such as the target thyroid function for pregnant hypothyroid women on L-T_4 treatment. However, several aspects of some of the responders' clinical practice were contradictory to the guidelines, most notably universal screening of pregnant women for thyroid dysfunction.

Maternal thyroid hormones play an important role in the early fetal neurological development (8), and maternal hypothyroidism diagnosed in pregnancy should be corrected as promptly as possible (4, 7). Therefore, although most responders initiated full replacement dose of L-T_4 (based on variable regimes) for pregnant women newly diagnosed with overt hypothyroidism, it is unfortunate that a small minority still started on a small dose of L-T_4 (Table 1). Furthermore, despite the absence of published studies to support, most responders (89%) perceived that overt maternal hypothyroidism diagnosed in late first trimester leads to subtle or clinically significant neuropsychological impairment of the offspring even if the

Table 4 Target thyroid function test results in hypothyroid pregnant women on L-thyroxine replacement.

Targets	Responders *n* (%)
TSH and FT_4 within laboratory reference range	13 (8.1)
TSH and FT_4 within the trimester-specific reference range	48 (29.8)
TSH <2.5 mIU/l in the first trimester and <3 mIU/l in the second and third trimesters	91 (56.6)
Other variable TSH, FT_4, and FT_3 targets	9 (5.6)

woman is adequately treated with L-T_4. Indeed, a study has found that IQs of the children whose mothers had been hypothyroid during early pregnancy were normal and similar to those of their siblings who were not exposed to maternal hypothyroidism *in utero* (9). Therefore, it is remarkable that a quarter of responders would recommend or discuss the option of abortion in such a situation.

It is well known that most hypothyroid women need an increased dose of L-T_4 from very early pregnancy (10). Indeed, about 25% women on L-T_4 replacement have biochemical evidence of under replacement at their first antenatal visit (11), which may be prevented by optimizing the L-T_4 dose before pregnancy (12). Other recommended approaches include advising the woman to increase the dose of L-T_4 by 30–50% (10) or by two tablets per week (5) as soon as pregnancy is confirmed. In the absence of studies comparing these different approaches, this survey has highlighted inconsistency in clinicians' approach for optimizing L-T_4 replacement in hypothyroid women planning pregnancy (Table 2). For hypothyroid women undergoing ovarian hyperstimulation, there was an increased trend to optimize the dose of L-T_4 before the procedure (Table 2), an approach supported by studies showing a rapid increase in TSH level in hypothyroid women who become pregnant following ovarian hyperstimulation (13). There was, however, general consensus on the target thyroid function for pregnant hypothyroid women on L-T_4 with most responders (86%) aiming to achieve TSH and FT_4 within the trimester-specific reference range or TSH <2.5 mU/l in the first trimester and <3 mU/l in the later trimesters (Table 4), as recommended by the guidelines (4, 7).

Whether all pregnant women should be screened for thyroid dysfunction has been hotly debated in recent years (14), and the lack of consensus on the issue has been reflected in this survey. The debate is fueled by increasing evidence for the association between mild maternal thyroid hormone deficiency in pregnancy and impaired neuropsychological development of the offspring (15–17) as well as other adverse obstetric outcomes (18). However, evidence from randomized controlled trials showing that L-T_4 replacement prevents neuropsychological impairment of the offspring is still lacking. A single randomized controlled trial has suggested that identification of mild thyroid hormone deficiency in the low-risk pregnant women by screening and treatment with L-T_4 may reduce obstetric complications (6). The Endocrine Society Guidelines as well as the recent ATA guidelines do not advocate universal screening, but recommend targeted case-finding of the high-risk pregnant women (4, 7); however, several studies have shown that the targeted case-finding approach misses a significant proportion of pregnant women with thyroid dysfunction (6, 11). Therefore, it is remarkable that, contrary to the recommendations of the guidelines, 40% of the responders or their institutions carry out universal screening of pregnant women for thyroid dysfunction.

This survey has also highlighted several other uncertainties surrounding screening thyroid function in pregnancy, including timing, tests, and criteria for starting treatment. It is noteworthy that two-thirds of the responders reported that they screened thyroid function during pre-pregnancy visit. One could argue that the identification and treatment of hypothyroidism in the first antenatal visit, as recommended by the guidelines (4, 7), may be too late to prevent the associated adverse effects; however, implementing systemic screening of thyroid function in all women contemplating pregnancy would be an enormous challenge for any country. Although a recent study has suggested that, if screening is limited to first trimester, over 40% pregnant women with hypothyroidism could be missed (19), there was no agreement amongst responders whether thyroid function tests should be routinely repeated in later stages of pregnancy if the initial screening was normal.

This survey demonstrates a lack of consensus on when to start L-T_4 following the screening, although about half of the responders would start L-T_4 if TSH is above 2.5 mU/l. Although a recent study has shown an increased risk of miscarriage in TPO-Ab-negative women with TSH 2.5–5 mU/l (20), there is no

Table 5 Risk factors used by responders carrying out targeted screening of pregnant women for thyroid dysfunction to stratify the high-risk group.

Risk factors	Responders *n* (%)
Personal history of a thyroid disease	59 (96.7)
Personal history of an autoimmune disease	55 (90.2)
History of a thyroid disease in first degree relatives	50 (82.0)
Presence of a goiter	56 (91.8)
History of neck irradiation	53 (86.9)
Previous thyroid surgery	54 (88.5)
Obesity	11 (18.0)
Family history of an autoimmune disease	38 (62.3)
History of miscarriage	55 (90.2)
History of infertility	49 (80.3)
Notion of inadequate iodine nutrition	30 (49.2)

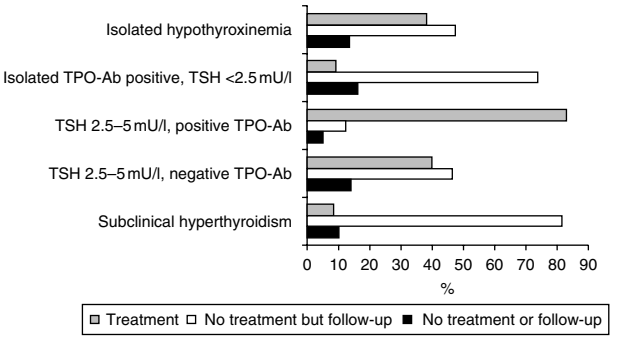

Figure 1 Percentage of responders recommending treatment, follow-up only or no action for various outcomes following thyroid screening in pregnancy.

randomized controlled trial evidence to show benefit of L-T_4 in these women. In contrast, there is growing evidence for an association between thyroid autoimmunity and adverse obstetric outcomes such as miscarriage and preterm delivery (21), and a randomized controlled trial has shown that L-T_4 may reduce these adverse outcomes in euthyroid TPO-Ab-positive pregnant women (22). Interestingly, most responders (90%) would not treat euthyroid pregnant women with TPO-Ab (Fig. 1). This practice is in agreement with the Endocrine Society Guidelines, which do not recommend L-T_4 for these pregnant women (4). Likewise, the recent ATA guidelines have found insufficient evidence to recommend for or against L-T_4 replacement for these women (7), underlining the need for further studies.

This survey has echoed the prevailing lack of consensus on the definition and management of isolated maternal hypothyroxinemia (23). Although maternal hypothyroxinemia has been shown to be associated with impaired neuropsychological development of offspring (17), there is a lack of randomized controlled trials showing a benefit of L-T_4 in this condition. Furthermore, a large observational study has failed to show an association between maternal hypothyroxinemia and obstetric adverse outcomes (24). Despite these observations and contrary to the recent ATA guidelines recommending against the treatment of maternal hypothyroxinemia in pregnancy (7), it is remarkable that nearly 40% of the responders reported that they would treat isolated maternal hypothyroxinemia.

We acknowledge several limitations of this survey. First, most of the responders of the survey are endocrinologists, and it is possible that their approach to the management of hypothyroidism in pregnancy is different from that of other healthcare professionals, including obstetricians. Secondly, clinical practices of members of a learned thyroid association may differ from those of non-member endocrinologists. Finally, variation in the clinical practices in different countries could have influenced the overall results of the survey. The small number of responders from each individual country precluded analysis of the potential geographical differences. Nevertheless, with responders from 28 European countries, we believe that this survey provides a snapshot of current trends in the management of hypothyroidism during pregnancy in Europe, and demonstrates further that clinicians often do not adhere to clinical practice guidelines (25).

In conclusion, this survey demonstrates a lack of consensus in the treatment and screening of maternal hypothyroidism during pregnancy in Europe, and highlights the need for further studies to promote evidence-based clinical practice and reduce variability in the care.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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