

Identifying and treating subclinical thyroid dysfunction in pregnancy: emerging controversies

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Abstract

Thyroid hormones are essential for an adequate growth and development of the fetus. In addition to the classical association between maternal hypothyroidism and neurological impairment in the progeny, other adverse reproductive events have been associated with maternal thyroid dysfunction including infertility, miscarriage and preterm delivery. Although all scientific societies endorse the treatment of overt hypothyroidism; the management and/or treatment of subclinical hypothyroidism, hypothyroxinemia or antithyroid antibody-positive women should be considered with caution. Important trials have found no clear benefit of treatment of subclinical hypothyroidism in terms of cognitive outcomes; however, other interventional studies appear to reduce some of the obstetric and perinatal complications. As a result, the dilemma between universal screening or selective screening of women at high risk of thyroid dysfunction during pregnancy remains unresolved. Despite this, levothyroxine is also now regularly prescribed by gynaecologists and centres for reproductive medicine. In this context, there is increasing concern regarding the risk of over diagnosis and subsequent potential overtreatment. Taken together, we need to reconsider how thyroid dysfunction should be identified in pregnant women and highlight the arguments for and against the use of levothyroxine in obstetric practices. Our main findings: the mismatch between the guidelines recommendations and the use of LT4 in clinical settings as well as the disparity of criteria between scientific societies from different medical specialties. In conclusion, it is essential to reach agreements between both endocrinologists and obstetricians.

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Introduction

Over the last two decades, we have witnessed a revolution in our knowledge of the role of thyroid hormones in intrauterine stages of development (1). However, important uncertainties remain regarding both the screening and management of maternal thyroid status in optimising perinatal outcomes (2, 3).

Different clinical guidelines have been published by scientific societies in a relatively short period of time (4, 5, 6, 7), trying to shed light on the most burning questions whilst two important trials were carried out (8, 9). However, the absence of clear evidence of the

effectiveness of treatment of subclinical hypothyroidism on child cognition, contrasts with promising results for other reproductive outcomes such as preterm delivery (10) or miscarriage (11, 12).

But the striking paradox is that whilst the scientists search for stronger evidence, clinicians are increasingly using levothyroxine empirically (13, 14).

Our aim has therefore been to summarise complementary and sometimes contradictory viewpoints around the assessment of thyroid function during pregnancy and the subsequent management of thyroid disease.

Reasons for universal screening

Universal screening for thyroid function at early stages of gestation has become a recurrent controversy in the scientific literature (2, 15) and has even generated interest in the general population (16). In spite of the fact that scientific societies do not recommend this clinical approach during pregnancy at present, the most recent clinical guidelines address how to interpret and manage thyroid diseases that might have only been identified by effective universal screening (4, 5, 6, 7).

In 2014, we published the arguments for universal screening (15) following the criteria established by Beaglehole (17): Is thyroid dysfunction during pregnancy really a health problem? Are simple and reliable diagnostic tests available? Is universal screening cost-effective? Is there a simple, safe and economically affordable treatment? And how and when should all of this occur?

Box 1: Criteria for screening by Wilson and Junger (18)

1. Is it an important health problem?
2. Is there an accepted treatment?
3. Are facilities for diagnosis and treatment available?
4. Is there should a recognizable latent stage where symptoms are lacking?
5. Is there should a suitable test or examination?
6. Is the test acceptable to the general population?
7. Is the natural history of the condition, including development from latent to declared disease understood?
8. Is there an agreed policy on whom to treat as patients?
9. Is the cost of case finding (including diagnosis and treatment of patients diagnosed) economically appropriate?
10. Case finding should be a continuing process and not a 'once and for all' project.

This should be considered as the 10 key criteria for screening set out by Wilson and Junger (18).

Careful analysis of these 10 criteria provides a persuasive case for universal thyroid screening in pregnancy. For criteria 1, it is well established that thyroid dysfunction, particularly overt thyroid disease in pregnancy is an important health problem. Treatment of both hypothyroidism and hyperthyroidism result in improved outcomes with treatment and testing being both acceptable and widely available (criteria 2, 3, 5 and 6). For hypothyroidism in particular, there is a well-recognised

latent asymptomatic stage (criteria 4 and 7). The cost of universal thyroid screening is favourable even if only the overt disease is considered (19); furthermore, the nature of screening in pregnancy ensures that it will be a continuous process (criterion 10). However, universal thyroid screening struggles to meet criterion 8 as a policy on whom to treat is yet to be agreed. Whilst all societies would recommend treatment of overt thyroid disease, there is much greater debate as to whether subclinical hypothyroidism and isolated hypothyroxinemia should be treated.

We will now study these arguments in more detail. The reasons for the implementation of a systematic determination of thyroid hormones at the first trimester of pregnancy might also be classified according to the purpose of the detection itself.

- For Endocrinology, the most obvious argument is the association of maternal overt hypothyroidism with obstetric and perinatal complications and the clinical impact of its early detection and treatment (20). Additionally, universal screening has shown to be more effective to detect all cases of thyroid dysfunction than targeted high-risk case-finding approach (21, 22). High-risk screening will miss the majority of cases.
- For Epidemiology, the relatively high prevalence of thyroid diseases in women (particularly at childbearing age) and their likelihood to be present in cases of infertility, recurrent miscarriages and other adverse events in obstetrical settings (23).
- For Medical Research in general, more and more investigation is currently focussed on the first '1000 days' from pregnancy until two years of life as a crucial stage in Epigenetics (24). In this regard, thyroid hormones play a pivotal role in metabolic regulation and neurodevelopment (25).
- For Health Economics, several studies have shown that the universal analysis of thyroid function is cost-effective in comparison with the study of targeted groups of pregnant women (19, 26).
- For Public Health, because pregnancy is considered a privileged condition for preventive actions and a window to address some health conditions lifelong (27). More recently, new factors have emerged that should be regarded:

1. The effectiveness of levothyroxine to ameliorate clinical pregnancy outcomes in women with subclinical hypothyroidism and/or thyroid autoimmunity undergoing assisted reproduction techniques (ART) and the dissemination of these results in reproductive medicine journals (28) has

led to the strict preconceptional adjustment of TSH levels in infertile women attempting conception (29). Levothyroxine therapy is becoming widespread among women undergoing *in vitro* fertilization even in euthyroid patients (30).

2. The acceptance of a thyroid-stimulating hormone (TSH) level of 2.5 U/L as the upper limit of normal of TSH at first trimester has resulted in a substantial increase in the number of women being classified as hypothyroid in different populations (31, 32). In fact, one of the most relevant changes from the 2011 guidelines of the American Thyroid Association (ATA) (33) to the 2017 guidelines (7) is that in the absence of specific population-based reference ranges, the upper reference limit of 4.0 U/L may be used instead of the previously recommended limit of 2.5 U/L for TSH. However, those clinicians who have been using the former cut-off over the last five or six years will need time to change their practice.
3. Some concern has been raised that overtreatment with levothyroxine might have a deleterious effect on neurological development (34).

These circumstances have created a new scenario where many pregnant women are receiving levothyroxine therapy in cases of mild thyroid dysfunction or in the absence of population-based trimester-specific reference ranges. Probably, it is time to think that a sensible approach to reduce the potential harmful effect of unnecessary or questionable treatments might be to implement responsible strategies of universal screening for thyroid diseases within the pregnancy surveillance programmes, promoting pluridisciplinary endocrinological/obstetrical approaches.

Even within those who endorse universal screening, it is not clear which test should be used and when to perform screening. The current guidelines recommend a single TSH test with reflex TPOAb if TSH is between 2.5 and 10 U/L, even though the elapsed time before the TPOAb determination might delay any intervention. This is particularly crucial as the first 12 weeks are critical for optimising neurological development.

If a possible therapy with levothyroxine could improve pregnancy outcomes, it should be started as soon as possible (or better still before conception), which reinforces the necessity to screen at least early in the first trimester, around 9–11 weeks of amenorrhoea coinciding with a blood test in the first trimester. Furthermore, the combination of screening for thyroid dysfunction and aneuploidies would substantially improve the acceptability, simplicity, ease of administration and cost of this approach.

Reasons against universal screening

An adequate assessment of thyroid function in pregnant women requires specific practicalities that cannot be underestimated (35).

First of all, the dynamic changes in thyroid function throughout gestation (32) and its complex relationship with human chorionic gonadotrophin (hCG) (36) results in gestational age as a key determining factor in interpreting the thyroid function tests correctly. Although the use of trimester-specific reference range is strongly recommended (7), they are not currently available in many centres or they are not based on local populations (37). Although this would rapidly change if universal screening was introduced.

This dynamic change in thyroid physiology is more relevant in the early stages of gestation and, consequently, TSH reference limits differ widely within the first trimester of pregnancy (38). Whilst the lower TSH in weeks 9–12 of pregnancy are evidently explained by the high hCG production, considerably higher TSH values were observed earlier than 6 weeks of gestation, which are similar to non-pregnancy reference limits. The use of thyroid tests in ignorance of gestational age can mislead their interpretation, so the same women can be classified in normal or pathological TSH values only depending on their gestational age at the time of thyroid test in first trimester (39).

Additionally, most European countries remain mildly iodine deficient, and this should be taken into account when American guidelines are applied in Europe. The iodine intake might explain differences in TSH values among populations and whilst it would be ideal to only use women with optimal iodine intake to establish reference ranges in pregnancy (7), this would be challenging to undertake in Europe in the immediate future. Women should be counselled to ensure adequate iodine status during pregnancy.

The measurement of T4 concentration is also affected by the assay technology varying significantly by manufacturer. Assay method-specific and trimester-specific reference ranges should be used for serum fT4, although other alternative methods have been proposed such as total T4 measurement or free thyroxine index (7).

Whilst the standardisation of thyroid function tests remains at present as an unattainable goal (40), the reference ranges are highly laboratory dependent and not applicable outside of its own clinical setting (37). In terms of pregnancy surveillance programmes, these factors need to be taken into consideration as laboratory

reproducibility cannot be guaranteed. It is important to remark that the validity and repeatability of these tests are strongly constrained by these factors.

We should also reflect on what is the purpose for the screening of thyroid function during pregnancy: to detect thyroid diseases and to prevent adverse outcomes (15). If the genuine objective of screening is to identify those women at risk for pregnancy and/or perinatal complications, maybe we should reinforce the search for certain subgroups of women with history of adverse reproductive events: previous infertility, recurrent miscarriages or preterm delivery. In this regard, the Practice Committee of the American Society for Reproductive Medicine (ASRM) (41) include recommendations for the screening for thyroid abnormalities to evaluate recurrent pregnancy loss, but they do not establish an upper limit for TSH in pregnancy, and they also found insufficient evidence to recommend routine thyroxine (T4) testing or screening for antithyroid antibodies. Additionally, the most recent preventive strategies for preterm delivery do not include thyroid dysfunction as a potential and preventable risk factor (42, 43).

Even if we would implement the systematic determination of TSH and T4 in all pregnancies, we would not be able to reduce the incidence of obstetric complications associated to autoimmune thyroid disease (AITD) (44). Although the universal antithyroid antibodies testing during pregnancy has been published to be cost-effective (19), its routine implementation in certain clinical settings (clinics, private practice) might not be appropriate in either economic or practical terms (45).

Additionally, the effectiveness of screening requires an early treatment in case of abnormal results of thyroid function tests. This would enforce the need for including the identification and management of thyroid dysfunction in pregnant women as competency of obstetricians and reproductive medicine specialists (46, 47).

In summary, before recommending a policy for universal screening of thyroid function at present, we should address our efforts to reach substantially closer agreements in management between endocrine and obstetric clinics.

In favour of treating subclinical thyroid dysfunction

The treatment in case of abnormal thyroid function test results ought to be a direct consequence of the universal screening policy. In this regard, levothyroxine

therapy is unanimously recommended in cases of overt hypothyroidism (4, 5, 6, 7). However, for subclinical hypothyroidism (SCH) or AITD, the recommendations from the guidelines have been experiencing frequent modifications to try to incorporate the best evidence available over the last decade.

Numerous observational studies and meta-analysis have demonstrated the association of SCH to adverse pregnancy and neonatal outcomes (Table 1) (48, 49, 50, 51, 52, 53, 54, 55, 56, 57), but the current guidelines show different recommendations for SCH: for ACOG (6) there is no evidence that identification and treatment of subclinical hypothyroidism during pregnancy improves outcomes. The Endocrine Society (4) and European Thyroid

Table 1 Meta-analysis and observational studies in cases of subclinical hypothyroidism in pregnancy.

| Study | Results | OR (95% CI) |
|------------------------------|--|------------------|
| Meta-analysis | | |
| (48) | Miscarriage/pregnancy loss | 1.90 (1.59–2.27) |
| (49) | Miscarriage/pregnancy loss | 2.01 (1.66–2.44) |
| | Preterm delivery | 1.20 (0.97–1.50) |
| | Growth restriction | 1.70 (0.83–3.50) |
| | Pre-eclampsia | 1.30 (1.00–1.68) |
| | Gestational diabetes | 1.28 (0.90–1.81) |
| (50) | Growth restriction | 1.54 (1.06–2.25) |
| (51) | Gestational diabetes | 1.56 (1.29–1.88) |
| (52) | Gestational diabetes | 1.39 (1.07–1.79) |
| (53) | Pre-eclampsia | 1.70 (1.10–2.64) |
| | Gestational diabetes | 1.40 (0.64–2.80) |
| | Perinatal mortality | 2.7 (1.60–4.72) |
| Total range for OR: | | |
| | Miscarriage | 1.90–2.01 |
| | Preterm delivery | 1.20–1.81 |
| | Growth restriction | 1.54–3.36 |
| | Pre-eclampsia | 1.30–2.24 |
| | Gestational diabetes | 1.28–4.33 |
| Observational studies | | |
| (54) | Gestational diabetes | 1.81 (1.08–1.73) |
| (55) | Preterm delivery | 1.81 (1.02–3.28) |
| (56) | Pre-eclampsia | 2.24 (1.25–4.02) |
| | Growth restriction | 3.36 (1.75–6.38) |
| (57) | Growth restriction | 3.10 (1.22–8.01) |
| | Gestational diabetes | 4.33 (2.10–8.91) |
| TSH upper limit (mIU/L) | | |
| | Screening before 20 weeks of gestation | 4.08 |
| | Screening before 14 weeks of gestation | 2.5 |
| | Screening at any moment during pregnancy | |
| | 1st trimester | 3.47 |
| | 2nd trimester | 3.81 |
| | 3rd trimester | 4.99 |
| | Screening before 15 weeks of gestation | 2.53 |

Association (ETA) (5) guidelines endorse levothyroxine replacement independent of the presence of thyroid antibodies, although the recommendation level for obstetrical outcomes is weaker in women with SCH who are TPO Ab negative (Table 2). The new ATA guidelines (7) recommends, first, the evaluation of thyroperoxidase antibody (TPOAb) status in pregnant women with TSH concentrations >2.5IU/L. Levothyroxine therapy is recommended for women who are positive for TPO-Abs with TSH greater than the pregnancy-specific reference range (strong recommendation, moderate quality evidence) and may be considered with TSH concentrations >2.5IU/L and below the upper limit of the pregnancy-specific reference range (weak recommendation, moderate quality evidence).

The recent ATA guidelines have taken into account that the combination of SCH and AITD is more likely to be associated with poorer obstetric outcomes (58, 59). This recommendation is supported by the most recent findings concerning the interrelationship between SCH and AITD: out of all TPOAb-positive women, those with the lowest TSH suppression by hCG have higher risk of adverse pregnancy outcomes than those women who respond to hCG stimulation normally (60).

When the interventional studies with levothyroxine performed so far are reviewed (Table 3) (61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76), they seem to be more effective in preventing adverse obstetric events (mainly miscarriage and preterm delivery) in cases where AITD was present. All these studies have provided us with a more precise understanding of how to identify women at risk of developing pregnancy complications and will probably lead to better indications for therapy and consequently, more effective treatments. In this regard, systematic screening for TSH and TPOAb in women with a history of infertility or recurrent pregnancy losses needs to be considered, ideally before conception for maximum benefit.

For TPOAb-positive euthyroid women, the use of thyroxine might be offered individually in cases of assisted reproductive techniques (ART) (7), history of recurrent miscarriage (65) or preterm delivery (76), but there is no evidence of benefit in any other obstetric complications.

The identification of these targeted groups of women at risk of adverse outcomes should be considered by reproductive medicine specialists as a priority, since thyroid dysfunction can jeopardize pregnancy viability and early treatment might substantially improve the rates of successfully completed pregnancies (65, 76).

Recurrent miscarriage and preterm delivery are highly prevalent entities in Obstetrics (39, 40, 41), which result in tremendous social and economic burdens (77, 78). At present, much effort is being invested in order to reduce their impact on families and health services. In this regard, the recent results of levothyroxine use in reducing pregnancy loss and preterm delivery are certainly promising (11, 76). However, it is important to highlight that all the interventions with levothyroxine (LT4) replacement performed to date did not include any other preventive or therapeutic approach: data are lacking regarding the effectiveness of LT4 in combination with aspirin for recurrent miscarriages or progesterone and/or pessary for preterm delivery; and these approaches should be evaluated through further studies.

It might be argued that levothyroxine therapy is indicated in select cases of mild thyroid hypofunction during pregnancy and its effectiveness in preventing obstetric complications might be greater if earlier onset, association to other drugs and dosage adjustment are optimized (79).

In summary, the indications for LT4 therapy needs to be considered, taking into account the evidence available and on a case-by-case assessment of obstetric risk factors (Table 2).

Against treating subclinical thyroid dysfunction

There are solid arguments to treat overt hypothyroidism at any stage of life and, particularly, during pregnancy in order to prevent serious adverse effects to the fetus (80). Nevertheless, a worrying percentage of levothyroxine-treated women do not receive a careful preconception adjustment to optimize thyroid function before pregnancy (81) or advice to use contraception until achievement of a euthyroid state before conceiving (82) or even they demonstrate low adherence to treatment during pregnancy (83). According to this, it would seem more reasonable to persevere with the optimization of treatment for overt hypothyroidism during the preconception stage and at early gestation than focus attention on subtle alterations in thyroid function tests (84).

Furthermore, two large-scale trials were carried out to investigate the effectiveness of levothyroxine therapy during pregnancy to ameliorate the cognitive function in children (8, 9). None of these studies have shown a significant effect of LT₄ on preventing adverse cognitive outcomes, though both studies performed a late

Table 2 Indications for treatment with levothyroxine during pregnancy according to the main outcomes.

| | Recommendation | Pros | Cons |
|--|-------------------------------------|--|--|
| Pregnancy outcomes | | | |
| TPOAb positive | | | |
| TSH >10IU/L | LT4 therapy is strongly recommended | Treatment of overt hypothyroidism reduces the risk of pregnancy complications | None |
| TSH 4.0–10.0IU/L | LT4 therapy is recommended | Treatment in this group reduces the risk of pregnancy complications and evolution to overt hypothyroidism | LT4 therapy need to be monitored in order to avoid sub/overtreatment |
| TSH 2.5–4.0IU/L | LT4 therapy may be considered | Treatment should be restricted to high risk of pregnancy complications such as infertility or recurrent pregnancy loss (weak evidence for preterm delivery) | - Weak recommendation - High risk of overtreatment - No evidence of effectiveness for: <ul style="list-style-type: none"> • Gestational diabetes • Hypertensive disorders • Growth restriction |
| TSH <2.5IU/L | LT4 therapy is not recommended | Treatment should be restricted to high risk of pregnancy complications such as infertility, ART or recurrent pregnancy loss and considered on a case-by-case basis | There is insufficient evidence to conclusively determine if LT4 therapy improves fertility or decreases pregnancy loss risk in TPOAb positive, euthyroid women |
| TPOAb negative | | | |
| TSH >10IU/L | LT4 therapy is strongly recommended | TSH >10IU/L can be considered as overt hypothyroidism | The quality of evidence is low |
| TSH 4.0–10.0IU/L | LT4 therapy is recommended | Similar adverse risk to SCH and TPOAb positive when TSH exceeds 5–10IU/L | - Weak recommendation - The quality of evidence is low - Treatment should be considered with caution if reference ranges are not available |
| TSH 2.5–4.0IU/L | LT4 therapy should not be used | Low dose LT4 can be used in women undergoing IVF or ICSI, in order to achieve a TSH <2.5IU/L | There is insufficient evidence to determine if LT4 therapy improves fertility in TPOAb negative, euthyroid women |
| TSH <2.5IU/L | LT4 therapy is not recommended | None | - Strong recommendation against the use of LT4 in this situation - Potential risks of iatrogenic use of thyroxine in pregnancy: <ul style="list-style-type: none"> • Growth restriction • Abnormal brain morphology in children |
| Cognitive function in offspring | | | |
| TSH >10IU/L | LT4 therapy is strongly recommended | Untreated high TSH levels have been associated to lower IQ scores, independently of the test | The effectiveness of LT4 therapy on fetal neurodevelopment is limited to an early intervention (during first trimester) |
| TSH 4.0–10.0IU/L | LT4 therapy is recommended | Early onset of LT4 treatment can improve cognitive function in offspring | The effectiveness of LT4 treatment has not yet conclusively demonstrated in terms of cognitive outcomes |
| TSH 2.5–4.0IU/L | LT4 therapy should not be used | None | - High risk of overtreatment - No evidence of effectiveness on cognitive outcomes |
| TSH <2.5IU/L | LT4 therapy is not recommended | None | - Strong recommendation against the use of LT4 in this situation- Potential risks of iatrogenic use of thyroxine in pregnancy: <ul style="list-style-type: none"> • Growth restriction • Abnormal brain morphology in children |

intervention (at the end of first trimester or later), which might limit their effectiveness when compared with early treatment (85). Some interventional studies with levothyroxine offered optimistic findings (Table 3), but others have not found significant differences in adverse pregnancy events between treated and untreated groups (14, 71, 73, 75) in cases of SCH and/or AITD.

Before considering levothyroxine therapy in cases of mild thyroid dysfunction, we should review how many shortcomings are present in this recommendation. First of all, we need reliable diagnostic criteria to identify SCH properly, specifically adjusted by gestational age and population based. As we have previously indicated, the availability of own reference ranges is the real Achilles' heel for a responsible screening policy in many centres. After that, a search for TPO antibodies should be done, in order to determine the existence of autoimmunity, according to the recent ATA guidelines (7); therefore, the onset of treatment and its potential effectiveness would be conditioned to the elapsed time until the complete assessment of thyroid function.

In clinical settings, where reference range are not available, the treatment for SCH should be considered with caution (TSH >4IU/L or TPOAb positive with TSH >2.5IU/L) (7). Although the use of thyroxine might potentially reduce miscarriage or preterm delivery rates, there is no evidence of effectiveness for gestational diabetes, hypertensive disorders (10) or infant cognitive function (8, 9). The use of levothyroxine in case of AITD with normal thyroid function is not currently recommended by any scientific society (4, 5, 6, 7), although ATA guidelines consider the use of thyroxine in cases of TPOAb positive with TSH >2.5IU/L.

However, a TSH cut-off of 2.5IU/L or 4.5IU/L in women who underwent *in vitro* fertilisation (FIV) (86) or intrauterine insemination (87) did not show differences in the rates of clinical pregnancy, delivery or miscarriage. These results are in consonance with the hypothesis that the risk of adverse pregnancy outcomes is lower in women with a relatively normal response to hCG (60) as must occur in successful cycles in assisted reproduction. The empirical use of levothyroxine in women with history of infertility or before ART is not currently justified.

Finally, the risk of overtreatment has become a concerning issue inherent to the overuse of levothyroxine in obstetric practices (88, 89). Regarding the effects of additional levothyroxine supply on the fetus, there are no currently available fetal markers to monitor the

utero-placental passage of LT₄ (90). However, samples of fetal blood obtained by cordocentesis showed free T₄ levels concentrations higher than normal levels in around 60% of fetuses from euthyroid mothers with AITD who had received levothyroxine (91). Thyroid hormones would have a U-shaped effect on fetal development, particularly the fetal brain development so as both deficiency and excess might impair fetal neurodevelopment (25). High maternal free LT₄ concentrations have been associated to lower child IQ and lower grey matter and cortex volume (34).

The high free LT₄ levels in maternal blood have also been associated to low birth weight and an increased risk for small for gestational age (SGA) newborns (92). Additionally, a recent national survey in USA showed that thyroid hormone treatment was associated with decreased risk of pregnancy loss in women with subclinical hypothyroidism, but increased risk of other pregnancy-related adverse outcomes such as preterm delivery, gestational diabetes or pre-eclampsia (11). All these data highlight the need of selective indications of therapy, based on sensible treatment threshold for women who have mildly increased TSH without other risk factors.

In summary, it is highly likely that both overt hypothyroidism and the combination of subclinical hypothyroidism and TPOAb positivity may jeopardize pregnancy outcomes and which detection and treatment with LT₄ would ameliorate. Nevertheless, the need of treatment in cases of mild SCH with TPOAbs negative remains controversial, particularly with regard to cognitive outcomes.

Further scientific evidence is needed regarding the effectiveness of LT₄ therapy in euthyroid, TPOAbs-positive women in improving fertility in cases of ART, as well as in preventing miscarriage and/or preterm delivery. In this regard, new randomized controlled trials with timely onset of treatment with LT₄ are expected.

Conclusion

In order to increase the safety and effectiveness of levothyroxine treatment in obstetric practices, some key issues have to be addressed: the establishment of well-defined criteria for diagnosis adapted to every single population, laboratory and trimester of gestation; the acquisition of management skills in interpreting abnormal thyroid function tests by obstetricians; the inclusion of

Table 3 Interventional studies with levothyroxine in subclinical hypothyroidism and/or thyroid autoimmunity during pregnancy.

| Study | Design | Intervention | Results | Comments |
|-------|----------------------------|---|--|---|
| (61) | Meta-analysis | Studies on SCH included: (62), (58); 5 studies reported on the effect of LT ₄ therapy for AITD | SCH: ↓ Miscarriage, ↓ Preterm delivery, TAI: Miscarriage (not significant), ↓ Preterm delivery | Conclusion: For SCH and AITD, evidence is insufficient to recommend treatment with thyroxine |
| (14) | Prospective Non-randomised | 53 pregnancies from 34 patients TPO Ab (+) with recurrent miscarriage: - 17 pregnancies with LT ₄ treatment - 36 pregnancies without treatment | No significant difference in the outcome between groups in live birth rate | Empirical thyroxine therapy in TPOAb(+) pregnant women did not seem to improve outcome |
| (63) | Retrospective | 96 TPO Ab (+) pregnant women - 49 treated with LT ₄ - 47 no treated | ↓ Miscarriage rate | Potential benefit of universal screening and LT ₄ treatment in pregnant women with TAI |
| (10) | Meta-analysis | Studies on SCH included: (64), N (65), (66) (67) | ↓ Preterm delivery, No effect on pre-eclampsia | There was a trend towards reduced risk of miscarriage with LT ₄ , but did not reach statistical significance |
| (28) | Meta-analysis | Studies on women with SCH undergoing ART included: (68), (69), (70) | ↑ Delivery rate, ↓ Miscarriage rate | In an ART setting, no data are available on the effects of LT ₄ treatment on preterm delivery or pre-eclampsia |
| (71) | Prospective Non-randomised | Women with SCH and history of recurrent early pregnancy loss -24 treated with LT ₄ -15 no treated | No significant difference in the outcome between groups in live birth rate | The prevalence of SCH in thisREPL cohort was 19% |
| (72) | Prospective Non-randomised | Cost-effectiveness analysis of screening and treatment after SpA 73 SCH and/or TAI treated with LT ₄ 38 SCH and/or TAI untreated | ↑ Successfully completed subsequent pregnancies | Screening for thyroid disorders in women after SpA and treatment with LT ₄ is cost-saving and it improves the subsequent pregnancy rate |
| (73) | Prospective Non-randomised | Women with 2 or more consecutive miscarriages 31 with AITD and 27 with SCH were treated with LT ₄ compared to 100 healthy women without a history of miscarriage | Following LT ₄ treatment, No difference in miscarriage rate between hypothyroid and euthyroid individuals in TPO Ab (+) women | The prevalence of AITD was higher in pregnant women with a history of recurrent miscarriage compared with healthy pregnant control population |
| (12) | Prospective Non-randomised | Screening group (675 pregnancies) was compared to control group (996 pregnancies) 105 SCH from screening group were treated with LT ₄ 252 SCH from control group did not receive treatment | ↓ Miscarriage rate, ↓ Fetal macrosomia risk, ↑ Cesarean risk | Screening and intervention of SCH can reduce the risk of miscarriage No significant differences were observed in other pregnancy outcomes between the two groups |
| (74) | Retrospective | 82 women with SCH were treated 284 women with SCH did not receive treatment with LT ₄ | ↓ Risk of low birth weight, ↓ Risk of low Apgar score | Other pregnancy-related adverse outcomes were similar between the two groups |
| (75) | Prospective Randomised | 198 euthyroid, AITD (+) treated with LT ₄ 195 euthyroid, AITD (+) untreated 197 euthyroid, AITD (-) untreated | No significant difference in miscarriage or preterm delivery rate between the 3 groups | Levothyroxine intervention had no impact on the rate of miscarriage or preterm delivery in euthyroid TAI (+) women |
| (76) | Prospective Randomised | 65 TPO Ab (+) women treated with LT ₄ 66 TPO Ab (+) women untreated. 131 TPO Ab (-) women untreated | ↓ Preterm delivery rate | The number needed to treat (NNT) for preterm birth was 1.7 |
| (11) | Retrospective | 843 women with SCH were treated 4562 women with SCH did not receive treatment with LT ₄ | ↓ Pregnancy loss, ↑ Preterm delivery, ↑ Gestational diabetes, ↑ Pre-eclampsia | The adjusted odd of pregnancy loss were lower in treated women than in untreated women if their pre-treatment TSH concentration was 4.1–10 mIU/L |

thyroid dysfunction as plausible cause for some obstetric complications in the algorithms in clinical decision-making and to have more joint endocrine and obstetric clinics. Each of these conditions needs substantial progress at present.

Details of ethics approval

The authors declare compliance with ethical standards for reviews.

Declaration of interest

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

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