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DEBATE: 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 foetus. 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. As conclusion, it is essential to reach agreements between both endocrinologists and obstetricians.

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 (4-7), trying to shed light into the most burning questions while two important trials were carried out (8, 9). However, the absence of clear evidence for the effectiveness of treatment of subclinical hypothyroidism on child cognition, contrasts with the 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 only been identified under circumstances of an effective universal screening (4-7).

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? Do we have available simple and reliable diagnostic tests? 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.

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 should 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 10 key criteria for screening set out by Wilson and Junger (18).

Careful analysis of these 10 criteria does in the main provide 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 results in improved outcomes with treatment and testing being both acceptable and widely available (criterias 2, 3, 5 and 6). For hypothyroidism in particular there is a well-recognised latent asymptomatic stage (criterias 4 and 7). The cost of universal thyroid screening is favourable even if only overt disease is considered (19); furthermore the nature of screening in pregnancy ensures it will be a continuous process (criteria 10). However universal thyroid screening struggles to meet criteria 8 an agreed policy on whom to treat. 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 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 and 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, since more and more investigation is currently focussed in 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:

a) 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). And levothyroxine therapy is becoming widespread among women undergoing in vitro fertilization even in euthyroid patients (30).

b) The acceptance of a thyroid-stimulating hormone (TSH) level of 2.5 mU/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 mU/L may be used instead of the previously recommended limit of 2.5 mU/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 chance their practice.

c) Some concern has been raised that over-treatment 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 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 programs, 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 2.5-10 mU/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 amenorrhea coinciding with blood test in 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 determinant 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 centers 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 what 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 in 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).

While 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 anti-thyroid 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 routinely implementation in certain clinical settings (clinics, private practice), might not be appropriate in economic neither or practical terms (45).

Finally, the effectiveness of screening is also conditioned to promptly treatment of abnormal thyroid function tests. This would enforce the need of 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 of 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 (4-7). 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) (48-57), 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 Association (ETA) (5) guidelines endorse levothyroxine replacement independently 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, firstly, the evaluation of thyoperoxidase antibody (TPOAb) status in pregnant women with TSH concentrations > 2,5 mUI/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 >2,5 mUI/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) (61-76), they seem to be more effective to prevent 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 pregnancy complications and probably will lead to better indications of 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 need 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 the early treatment might substantially improve the rates of successfully completed pregnancies (65, 76).

Recurrent miscarriage and preterm delivery are highly prevalent entities in Obstetrics (39-41), which result in tremendous social and economic burdens (77, 78). At present many efforts are being invested in order to reduce their impact in 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 approaches: 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 selected 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 need 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 carefully preconception adjustment to optimize thyroid function before pregnancy (81) or the 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 LT_4 on preventing adverse cognitive outcomes , though both studies performed a late 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 centers. 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); so 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 > 4mUI/L or TPOAb positive with TSH >2.5 mUI/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 (4-7), although ATA guidelines consider the use of thyroxine in cases of TPOAb positive with TSH >2.5 mUI/L.

However, the use a TSH cut-off of 2.5 mIU/L or 4.5 mIU/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 on the foetus of additional levothyroxine supply, there is no currently available fetal markers to monitor the utero-placental passage of LT_4 (90). However, samples of fetal blood obtained by cordocentesis showed free T4 levels concentrations higher than normal levels in around 60% of foetuses 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 LT_4 concentrations have been associated to lower child IQ and lower grey matter and cortex volume (34).

The high free LT_4 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 among 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.

It is needed further scientific evidence 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 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 need substantial progress at present.

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Table 1: Metaanalysis and observational studies in cases of Subclinical Hypothyroidism in pregnancy.

	Study	Results	Odd Ratio *(95% CI)*	Comments
Metaanalysis	*Zhang[48] (2017)*	Miscarriage/ Pregnancy loss	1,90 *(1,59-2,27)*	Total range for odd ratio: - 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
	Maraka[49] (2016)	Miscarriage/Pregnancy loss Preterm delivery Growth restriction Pre-eclampsia Gestational diabetes	2,01 *(1,66- 2,44)* 1,20 *(0,97- 1,50)* 1,70 *(0,83- 3,50)* 1,30 *(1,00- 1,68)* 1,28 *(0,90- 1,81)*	
	Tong[50] (2016)	Growth restriction	1,54 *(1,06- 2,25)*	
	Gong[51] (2016)	Gestational diabetes	1,56 *(1,29- 1,88)*	
	Toulis[52] (2014)	Gestational diabetes	1,39 *(1,07- 1,79)*	
	Van den Boogaard[53] (2011)	Pre-eclampsia Gestational diabetes Perinatal mortality	1,70 *(1,10- 2,64)* 1,40 *(0,64-2,80)* 2,7 *(1,60- 4,72)*	
Observational studies	*Ying[54] (2016*)	Gestational diabetes	1,81 *(1,08- 1,73)*	TSH upper limit: 4.08 mIU/L. Screening before 20 weeks of gestation.
	Arbib[55] (2016)	Preterm delivery	1,81 *(1,02- 3,28)*	TSH upper limit 2.5 mIU/L. Screening before 14 weeks of gestation.
	Chen[56] (2014)	Pre-eclampsia Growth restriction	2,24 *(1,25- 4,02)* 3,36 *(1,75- 6,38)*	TSH upper limit 3.47, 3.81 and 4.99 mIU/L in 1st, 2nd and 3rd trimester, respectively. Screening at any moment during pregnancy.
	Karakosta[57] (2012)	Growth restriction Gestational diabetes	3,10 *(1.22- 8.01)* 4,33*(2.10- 8.91)*	TSH upper limit 2.53 mIU/L. Screening before 15 weeks of gestation.

Note: Observational studies included in metaanalysis have not been reported in this table.

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

	Recommendation	Pros	Cons
PREGNANCY OUTCOMES ***TPOAb Positive***			
- TSH >10 mIU/L	LT4 therapy is strongly recommended	Treatment of overt hypothyroidism reduces the risk of pregnancy complications	None
- TSH 4.0-10.0 mIU/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- 4.0 mIU/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: • Gestational diabetes. • Hypertensive disorders • Growth restriction.
- TSH < 2.5 mIU/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 >10 mIU/L	LT4 therapy is strongly recommended	TSH >10 mUI/L can be considered as overt hypothyroidism.	The quality of evidence is low
- TSH 4.0-10.0 mIU/L	LT4 therapy is recommended	Similar adverse risk to SCH and TPOAb positive when TSH exceeds 5-10 mIU/L.	- Weak recommendation. - The quality of evidence is low. - Treatment should be considered with caution if reference ranges are not available.

- TSH 2.5- 4.0 mIU/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 <2.5 mIU/L	There is insufficient evidence to determine if LT4 therapy improves fertility in TPOAb negative, euthyroid women.
- TSH < 2.5 mIU/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: • Growth restriction • Abnormal brain morphology in children.
COGNITIVE FUNCTION IN OFFSPRING			
- TSH >10 mIU/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 4.0-10.0 mIU/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- 4.0 mIU/L	LT4 therapy should not be used	None	- High risk of overtreatment. - No evidence of effectiveness on cognitive outcomes.
- TSH < 2.5 mIU/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: • Growth restriction • Abnormal brain morphology in children.

Table 3: Interventional studies with levothyroxine in Subclinical Hypothyroidism and/or thyroid autoimmunity during pregnancy.

	Study design	Intervention	Results	Comments
Vissenberg et al (2012)[61]	Meta-analysis	Included Abalovich et al (2002)[62] and Negro et al (2010)[58] for SCH. Five 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.
Yan et al (2012)[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.
Lepoutre et al (2012)[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.
Reid et al (2013)[10]	Meta-analysis	For SCH included Rotondi et al (2004)[64], Negro et al (2006)[65], Negro et al (2007)[66] and Yassa (2010)[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.
Velkeniers et al (2013)[28]	Meta-analysis	Women with SCH undergoing ART. Included Negro et al (2005)[68], Abdel Rahman et al (2010)[69] and Kim et al (2011)[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.
Bernardi et al (2013)[71]	Prospective Non-randomised	Women with SCH and history of recurrent early pregnancy loss	NO significant difference in the outcome between groups in live	The prevalence of SCH in this recurrent early pregnancy loss

		-24 treated with LT_4. - 15 no treated.	birth rate.	(REPL) cohort was 19%.
Bartáková et al (2013)[72]	Prospective Non-randomised	Cost-effectiveness analysis of screening and treatment after spontaneous abortion (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.
Lata et al (2013)[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.
Ma et al (2015)[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.
Maraka et al (2016)[74]	Retrospective	82 women with SCH were treated. 284 women with SCH did not received 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.
Negro et al	Prospective	198 euthyroid, AITD (+) treated with LT_4.	NO significant difference in	Levothyroxine intervention had

(2016)[75]	Randomised	195 euthyroid, AITD (+) untreated. 197 euthyroid, AITD (-) untreated.	miscarriage or preterm delivery rate between the 3 groups.	no impact on the rate of miscarriage or preterm delivery in euthyroid TAI (+) women.
Nazarpour et al (2016)[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
Maraka et al (2017)[11]	Retrospective	843 women with HSC were treated. 4562 women with SCH did not received treatment with LT4.	↓ 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.