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JOANA FILIPA QUEIRÓS PEREIRA

Therapeutical approach to subclinical hypothyroidism during pregnancy

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Trabalho realizado sob a orientação de:

Prof. Dr. José Joaquim Sousa Barros

Dra. Helena Raquel Arantes Rodrigues Corte Real Gonçalves

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Therapeutical approach to subclinical hypothyroidism during pregnancy

Joana Pereira[2]; Helena Gonçalves[1], MD; José Barros[1], MD, PhD

1. Department of Obstetrics, Coimbra University and Hospital Center, Daniel de Matos Maternity Hospital, Portugal

2. Faculty of Medicine, University of Coimbra, Portugal

Prof. Dr. José Joaquim Sousa Barros

josebarros@huc.min-saude.pt

RESUMO

A gravidez é um estado capaz de induzir múltiplas alteações na fisiologia da glândula tiróide, levando a um aumento dos níveis de T3 e T4 durante toda a gestação e a uma diminuição nos níveis de TSH, dominante na primeira metade da gravidez (1–5). A importância das hormonas tiroideias para o desenvolvimento placentar e fetal já foi demonstrada em estudos animais e suportada por estudos em humanos (4). Existe uma prevalência de 2-3% de patologia tiroideia durante a gravidez e a avaliação da função tiroideia durante a gestação deve ser realizada por análise dos níveis de TSH e FT4 ou TT4, usando intervalos específicos para a população em questão ou, quando estes não estão disponíveis, os intervalos definidos pela ATA ou ETA (6–11).

O hipotiroidismo subclínico (HSC) representa uma forma moderada, compensada ou pré-clínica de hipotiroidismo primário e é definido por níveis elevados de TSH na presença de níveis normais de FT4 (12–15). Esta é considerada a patologia tiroideia mais prevalente durante a gravidez, com estudos sugerindo prevalências tão altas como 15% (8,14,16). As mulheres com HSC durante a gravidez podem ser assintomáticas, ou apresentar alguma sintomatologia fruste como cansaço e intolerância ao calor. Uma vez que estes sintomas podem ser relacionados com o estado gravídico por si só, o HSC tem um diagnóstico bioquímico (17). A principal causa de HSC em áreas cuja população não apresenta carência de iodo é a autoimunidade, estando especialmente relacionado com a presença de autoanticorpos TPOAb e TGAb (8). Embora a literatura possa demonstrar alguns resultados contraditórios, é bem aceite entre a população médica e científica que o HSC durante a gravidez está relacionado com consequências negativas para a mãe e feto, tais como aborto espontâneo, parto pré-termo, hipertensão gestacional, diabetes gestacional, pré-eclampsia, descolamento prematuro da placenta, índice Apgar baixo, baixo peso ao nascimento, morte perinatal e diminuição do QI na criança (17,18). Métodos de rastreio baseados numa abordagem universal ou numa estratégia oportunista estão a ser discutidos, no entanto, a maioria das associações cientificas reconhecidas continua a defender uma abordagem caso-a-caso (19,20).

Ao longo dos últimos anos, diferentes estudos têm sido publicados, tentando medir os benefícios da levotiroxina (LT4) no tratamento do HSC, com o objetivo de diminuir as suas consequências negativas durante a gravidez (21,22,31–34,23–30). A LT4 é um levo-isómero da tiroxina com a mesma atividade bioquímica que a hormona endógena e a sua utilização na gravidez é segura (35). Os estudos realizados em relação à LT4 apresentam alguns resultados contraditórios, com alguns concluindo a favor e outros contra a sua utilização no HSC (21,22,31–34,23–30). No que diz respeito à dose inicial que deve ser utilizada quando o tratamento é iniciado, e ao controlo do mesmo, estudos têm concluído que esta dose pode

ser definida sem ter em conta o nível de TSH inicial e que, independentemente da dose, testes de função tiroideia devem ser elaborados periodicamente e o ajuste de dose deve ser feito sempre que necessário(4,36–39).

A grande maioria dos estudos realizados mostra um claro benefício do tratamento do HSC durante a gravidez, especialmente por diminuir o risco de aborto espontâneo e parto pré-termo. Corroborando isto, as orientações da ATA e ETA recomendam o tratamento. Posto isto, cada país deve definir os seus próprios valores de referência, de modo a fazer um correto diagnóstico e tratamento do HSC durante a gravidez.(10,11)

Palavras-chave: gravidez, hormona estimulante da tiroide, hipotiroidismo subclínico, tratamento, levotiroxina

ABSTRACT

Pregnancy is a stage able to induce many physiological changes in thyroid gland leading to an increase in T3 and T4 levels during all pregnancy and a decrease in TSH levels, especially during the first half of pregnancy (1–5). The importance of thyroid function in placental and foetal development is supported by human data and has been demonstrated in animal models (4). Thyroid disease during pregnancy have an estimated prevalence of 2-3% and screening for thyroid hormone alterations in pregnancy must be performed by measuring TSH and FT4 or TT4 concentration using specific population-based pregnancy reference ranges or, when unavailable, ATA or ETA reference ranges (6–11).

SCH represents a mild, compensated or preclinical form of overt hypothyroidism and is defined as elevated TSH levels with normal FT4 (12–15). It is considered to be the most prevalent thyroid disorder during pregnancy with some studies finding prevalence as high as 15% (8,14,16). Pregnant women with SCH can be asymptomatic or present few symptoms of hypothyroidism such as fatigue or cold intolerance. Since these symptoms can be easily related to normal pregnant status, SCH is a biochemical diagnosed (17). The primary cause of SCH in iodine sufficient areas is autoimmunity, being especially related with auto-antibodies TPOAb and TGAb (8). Although literature can have some mixed results, it is well accepted among both medical and scientific population that SCH is related with negative pregnancy outcomes such as miscarriage, preterm delivery, gestational hypertension, gestational diabetes, pre-eclampsia, placental abruption, low Apgar score, LBW, neonatal death and decreased IQ in the offspring (17,18). An universal vs case-finding approach for screening thyroid disease during pregnancy keep being discussed, with the majority of the worldwide recognized associations defending a case-finding approach (19,20).

In order to lower the risk of negative outcomes related to SCH during pregnancy many studies have been performed on the last few years measuring the benefits on treating SCH with LT4 (21,22,31–34,23–30). LT4 is a levo-isomer of thyroxine with the same biochemical activity as the endogenous hormone and is proven to be safe during pregnancy and breast feeding (35). On the studies made for LT4 treatment during pregnancy there are some mixed results, with some studies favouring treatment and others against it (21,22,31–34,23–30). Concerning the dose that should be used and the management that should be done in pregnant women going through LT4 treatment, some different studies have shown that starting dose may not depend on TSH levels and, regardless the chosen starting dose, regular thyroid function tests must be performed and dose adjustment should be done (4,36–39).

Most of studies show a clear benefit on treating SCH during pregnancy, especially in lowering the risk for miscarriage and preterm delivery. Besides this, ATA and ETA guidelines support

the treatment of women with SCH during pregnancy. Hereupon, every country must define population-based cut offs for TSH levels in order to perform a correct diagnostic and treatment of SCH during pregnancy (10,11).

Key words: pregnancy, thyroid-stimulating hormone, subclinical hypothyroidism, treatment, levothyroxine

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LIST OF ABREVIATIONS

AACE	American Association of Clinical Endocrinologists
ART	Assisted Reproductive Technology
ATA	American Thyroid Association
BMI	Body Mass Index
CATS	Controlled Antenatal Thyroid Screening
D3	Deiodinase type 3 enzymes
ETA	European Thyroid Association
FT4	Free Thyroxine
HCG	Human Chorionic Gonadotropin
LBW	Low Birth Weight
LT4	Synthetic Levothyroxine
MoM	Multiple of the Median
NACB	US National Academy of Clinical Biochemistry
PROM	Premature Rupture of Membranes
SCH	Subclinical Hypothyroidism
T3	Triiodothyronine
T4	Thyroxine
TGAb	Anti-Thyroglobulin Antibodies
TGB	Thyroxin Binding Globulin
TPOAb	Anti-Thyroid Peroxidase Antibodies
TSH	Thyroid-Stimulating Hormone
TT3	Total Triiodothyronine
TT4	Total Thyroxine
WHO	World Health Organisation

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INTRODUCTION

Thyroid function during pregnancy

Pregnancy is a stage able to affect many endocrine functions and hypothalamic-pituitary-thyroid axis is no exception (1). Is well documented that a mild enlargement of the thyroid gland occurs which reflects the physiological changes (2). Placental human chorionic gonadotropin (HCG) peaks at 7-12 weeks of pregnancy causing an increase of oestrogen levels that will stimulate the liver to produce thyroxin binding globulin (TGB) and this will be maintained until the moment of delivery (3). On the other hand, the HCG itself has a weak thyrotrophic activity able to stimulate hormonal production in maternal thyroid gland. This will result in increased triiodothyronine (T3) and thyroxine (T4) levels during first trimester of pregnancy that will be maintained until the time of delivery (4,5). High T3 and T4 levels plus cross-reactivity of HCG to the thyroid-stimulating hormone (TSH) receptor on thyroid gland will result in significant lower TSH levels, especially during the first half of pregnancy (2). The placenta, rich in deiodinase type 3 enzymes (D3), metabolizes maternal thyroid hormones and the foetus receives relevant levels of those hormones in every stage of gestation, especially before endogenous foetal production which begins around 18 weeks (4).

The importance of thyroid function in placental and foetal development is supported by human data and has been demonstrated in animal models (4). It regulates migration, proliferation and differentiation of neuronal cells on the foetus, as well as myelination and synaptogenesis (40). Thyroxin also has a huge influence in foetal size and tissue maturation in preparation for life. Besides that, thyroid hormones directly affect uteroplacental development, henceforward they can influence pregnancy outcomes (4). *Colicchia et al.* has demonstrated that a local action of thyroid hormone on reproductive female organs and in early pregnancy during the embryo implantation is crucial for a successful pregnancy (41).

Thyroid disease during pregnancy

Pathological function of thyroid gland is 4 to 5 times more prevalent in women when compared to men, especially during fertile age (6). During pregnancy, at least 2-3% of women suffer from thyroid dysfunction and around 10% have autoimmune thyroid disease despite euthyroidism (5). There are three principal factors that influence thyroid function during pregnancy: the hormonal requirements, the supply of iodine, and the integrity of the gland (6). In iodine-sufficient populations the majority of thyroid disorders are owing to the autoimmune thyroid pathologies, namely Hashimoto´s thyroiditis and Grave's disease, even though iodine deficiency is the most common cause of gestational thyroid disfunction worldwide (7). Screening for thyroid alterations in nonpregnant adults consists of a TSH and eventual free T4

(FT4) evaluation levels (8). Due to changes in thyroid physiology, pregnant women need new reference ranges for T4 and TSH levels (2).

Serum TSH levels evaluation is the gold standard for assessment of thyroid function (3). Measurement of TSH by high sensitivity immunometric assays of third generation is the most accurate test, once it has a functional sensitive of 0.01 mU/L, wish is particularly useful to quantification of physiological low TSH concentration in early pregnancy (9). However, studies have shown that differences between analysis methods are not clinically significant (10). A descendant shift of the TSH reference levels occurs during pregnancy, with a reduction of about 0.1-0.2 mU/L on the lower limit and of about 0.5-1.0 mU/L on the upper limit. Once this decrease is mostly due to high HCG levels, it is important to notice that multiple pregnancies are expected to have a bigger reduction (10).

Even with this information, controversy continues about the upper limit of the normal reference range for TSH in iodine sufficient areas and population (9). The American Thyroid Association (ATA) released new guidelines in 2017 that have defined the upper TSH reference limit of 4.0mU/L (10). To defend this limit, analysis of the FT4 and TSH "set point" in pregnant women were made and showed that minor decreases in FT4 were observed only when the serum TSH level was greater than 4.8 mU/L (10). With regard to the lower limit, it is important to notice that subclinical hyperthyroidism has not been associated with bad outcomes in pregnancy and so is defined as "not clinically significant" (10). The European Thyroid Association (ETA) guidelines from 2014 suggests the following reference range: 0.1 to 2.5 mU/l to the first trimester; 0.2 to 3.0 mU/l to the second trimester; 0.3 to 3.0–3.5 mU/l to the third trimester (11). The authoritative US National Academy of Clinical Biochemistry (NACB) guidelines state that greater than 95% of healthy euthyroid pregnant woman have a serum TSH concentration between 0.4 and 2.5 mU/L (9). A study by Carty et al with 4643 pregnant women conclude that using a cut-off of 2.5 mU/l as upper limit to serum TSH concentration in pregnancy means that over 12% of subjects would be classified as having a thyroid disorder and treatment and monitoring of these women would have major economics and planning services implication (42). *Liu et al*. referred an increase in miscarriage in women with TSH levels between 5.22 and 10 mU/L. *Taylor et al*. found no increase in miscarriage if the TSH levels on the first trimester was less than 4.5 mU/L. These studies together suggest that a normal TSH upper cut-off of 2.5 to 3 mU/L may be too restrictive (8). Besides this controversy, it is accepted by all medical community that normal TSH ranges varies with age, gender, ethnicity, body mass index (BMI) and pregnancy status and population-based trimester laboratory ranges should be defined and applied if possible (10–12).

The measurement of FT4 in pregnancy is difficult, due to a decrease in albuminemia and a high circulation level of TBG (2,3). In addition, conventional immunoassays for measurement of FT4 are not well standardized for pregnancy, possibly leading to an inaccurate diagnosis (8). In one study of two commercially available immunoassays to measure FT4 levels, 70% of women were falsely diagnosed with low values (13). The FT4 index is an indirect calculation created to provide more reliable measurement of FT4 in pregnancy (8). Also, a solid-phase extraction liquid chromatography-tandem mass spectrometry method created seems to be reliable but is not widely available (2). Other systems of direct measurement, such as measurement by equilibrium dialysis or ultrafiltration, are less influenced by the pregnancy associated changes in serum proteins but are significantly more expensive (10).

The methodology used for total T4 (TT4) is more reliable, since only 0,03% of TT4 is unbound and TT4 levels are given in nanomolar range while FT4 are given in picomolar range (7). Although, changes in TT4 levels along pregnancy in euthyroid women have been previously showed, this changes are predictable, with an increase from weeks 7-16 in TT4 concentration that remain elevated until delivery and ultimately reaching 1,5 times the pre-pregnancy level (8,10,13). Therefore, an acceptable clinically upper level determination can be estimated by shifting the pre-pregnancy limit 50% higher when the measurement is made after 16 weeks of pregnancy (10,11). Otherwise, a calculation can be made based on increasing the pre-pregnancy reference limit by 5% per week, starting in week 7 (10). A study made by *Wilson et al*. conclude that when combined with TSH levels, FT4 or FF4 determinations using the common immunoassays are equally sensitive to identify women with thyroid disfunction (13). The most recent ATA guidelines recommend that when FT4 assay is used, method-specific and trimester specific pregnancy reference ranges should be applied. Otherwise, TT4 measurement is a reliable method to estimate hormone concentration in the last part of pregnancy (10). ETA recommendations from 2014 suggests that TT4 and FT4 assays are both suitable for thyroid function testing in pregnancy but trimester specific ranges should be established in each hospital based on their population (11).

Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) represents a mild, compensated or preclinical form of overt hypothyroidism and is defined as elevated TSH level with normal FT4 (12,14,15). Although, in theory, the diagnosis of SCH does not imply an upper TSH level as long as T4 remains within the normal range, the ATA, ETA and American Association of Clinical Endocrinologists (AACE) have recommended that any pregnant women with TSH level above 10mU/L and normal FT4 should be diagnosed and treated as having overt hypothyroidism (10,11,17). Pregnant women with SCH can be asymptomatic or present few symptoms of hypothyroidism such as cold intolerance and fatigue, symptoms that can be easily confused with normal pregnancy status

(21). Hereupon, SCH is a biochemical diagnosis and cannot be based on the symptoms presented by the patient (17). The prevalence of SCH varies largely rendering to local iodine status, trimester of pregnancy and TSH range used as diagnostic criteria (43). However, the vast majority of literature refers a prevalence of 2 to 3%, with some studies finding prevalence of 6.8% and even 15% (8,14,16).

For the last few years a huge number of studies have been made in order to define which are the complications associated with SCH (22). Results from various studies are indistinct mostly due to differences and limitations in study design, inadequacy of the population sample and nonstandardized definition of SCH (3,14). The most recent results have shown some association between SCH in pregnancy and multiple negative outcomes in the mother and the foetus, including spontaneous abortion, preterm birth, gestational hypertension, gestational diabetes, pre-eclampsia, placental abruption, low Apgar score, low birth weight (LBW), neonatal death and decreased IQ in the offspring (17,18). In 2009, *Benhadi et al.* reported a 60% increase in the rate of child loss for each doubling of TSH level above the normal range (44). Similarly, in 2010 *Negro et al.* found that women with TSH level between 2.5 and 5.0 mU/L had a 60% increase in miscarriage when compared with pregnant women whose TSH level was above 2.5 mU/L (9). *Ashoor et al*., in 2010, found that pregnant women who went through foetal loss had an increase in median TSH multiple of the median (MoM) and a decrease in FT4 MoM (5). In 2014, *Liu et al.* published a prospective cohort with pregnant women in the first trimester with TSH upper cut-off of 5.22 mU/L and did not found an increased risk of miscarriage with SCH in the absence of autoimmune factor (8). When studying another obstetrical complications and their association with SCH, *Casey et al*. (2005) demonstrated a significant association while *Cleary-Goldman et al.* (2008) and *Mannisto et al.* (2009) related these complications only with thyroid autoimmunity (5). In 2012, *Lazarus et al*., published a study showing no association between a low QI in children and SCH during pregnancy (8). More recently, *Maraka et al.* published, in 2015, a metanalysis concluding that SCH is associated with higher risk of pregnancy loss, placental abruption, premature rupture of membranes (PROM) and neonatal death (18). In the same year, *Chan et al.* published one other metanalysis with very similar results, showing a significantly increased risk of prematurity and placental abruption (4). **Table I** and **Table II** can clarify the latest principal metanalyses and observation studies, respectively, and their results.

Table I – Metanalyses about outcomes of SCH in pregnancy

Study	Year	Results	OR (95% CI)	Ref.
Toulis et al.	2014	Gestational diabetes	1.39 (1.07-1.79)	(45)
Chan et al.	2015	Prematurity	1.30 (1.05-1.60)	(4)
		Placental abruption	2.16 (1.15-4.06)	
Maraka et al.	2015	Miscarriage	2.01 (1.66-2.44)	(18)
		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)	
Tong et al.	2016	Growth restriction	1.54 (1.06-2.25)	(46)
Gong et al.	2016	Gestational diabetes	1.39 (1.07-1.79)	(47)
Van den Boogaard et al.	2016	Pré-eclampsia	1.70 (1.10-2.64)	(48)
		Gestacional diabetes	1.40 (0.64-2.80)	
		Perinatal mortality	2.7 (1.60-4.72)	
Zhang et al.	2017	Miscarriage	1.90 (1.59-2.27)	(49)

Table II – Observational studies about outcomes of SCH in pregnancy

Study	Year	Results	OR (95% CI)	Ref.
Wang et al.	2012	Spontaneous abortion	1.75 (1.05-2.90)	(50)
Karakosta et al.	2012	Gestational diabetes	1.81 (1.08-1.73)	(51)
Chen et al.	2014	Pre-eclampsia	2.24 (1.25-4.02)	(52)
		Growth restriction	3.36 (1.75-6.38)	
Ying et al.	2016	Gestational diabetes	1.81 (1.08-1.73)	(53)
Plowen et al.	2016	No association found		(54)
Arbib et al.	2017	Preterm delivery	1.81 (1.02-3.28)	(55)

In resume, even with some distinct results the vast majority of studies indicates that SCH in pregnancy comes with negative outcomes to the mother and foetus (56).

Anti-thyroid antibodies and Subclinical Hypothyroidism

The primary cause of SCH in iodine sufficient areas is autoimmunity (8). There are multiple anti-thyroid antibodies but the most common and well known are anti-thyroid peroxidase

antibodies (TPOAbs) and anti-thyroglobulin antibodies (TGAb). Around 5 to 15% of women in fertile age are positive for thyroid antibodies (8). In a study of 992 women who accessed a centre for infertility, the overall prevalence of autoimmunity for thyroid antibodies was 16%, with 8% having both antibodies, 5% having TGAb and 4% having TPOAb (17). Epidemiological studies made during the first two trimesters of pregnancy showed that 30-60% of pregnant women tested for TPOAb were positive (43). Although, only a proportion of women positive for thyroid auto-antibodies will have SCH and most will remain euthyroid (8). In a study realized by *Loh et al*. they found that TSH concentrations were significantly higher (2.0 vs 1.6 mU/L, p=0.04) and total T3 (TT3) concentrations were slightly lower (1,3 vs 1.4 pmol/L, p=0.032) in women with TPOAb antibodies when compared with those without TPOAb (14).

It is well known that in pregnant women who are euthyroid but are positive to TPOAb antibodies, there is a higher risk of miscarriage rates and preterm delivery (8). Hypotheses for this association can include differences in maternal thyroid hormone status, the proposition that anti-thyroid antibodies represent an epiphenomenon indictive of a generalized immune process or that this antibodies have a direct impact on the interaction between the foetus and placenta (2). Now, a systematic review have shown that the presence of autoimmune thyroid disease in women with SCH can increase the risk for preeclampsia and perinatal mortality, besides the association with miscarriage and preterm birth studied before (14,48). Due to the above-mentioned if TSH levels are raised, TPOAb should be measured to establish a diagnose of autoimmune thyroid disease and measurement of TGAb should too be considered (17). Though, postpartum thyroid disfunction can occur in 50% of these women, mostly manifested by postpartum thyroiditis (8). In this sense, TSH and FT4 concentrations should be measured six weeks postpartum (15). To finalize, it is important to notice that because pregnancy is a state of immunosuppression, thyroid antibody titters can decrease till 60% in the second half of pregnancy (17).

Iodine status and Subclinical Hypothyroidism

During pregnancy the iodine requirement is increased by about 50% due to a higher production of thyroid hormone, the exacerbation of renal loss of iodine by the increased glomerular filtration rate and the needs of the foetus to produce thyroid hormone in the second half of pregnancy (17). Both maternal and foetal hypothyroidism, in overt and subclinical forms, can result from severe to moderate iodine deficiency during pregnancy and led to an increase risk of congenital abnormalities and decreased IQ in children (2). Iodine deficiency can also raise the risk of poor obstetrical outcomes such abortion, prematurity and stillbirth (17). Low iodine levels are also indicated as the leading cause for isolated hypothyroxinaemia which can exert a negative influence in foetal brain development (5). Inadequate intake of iodine is seen in both developing and developed countries, with some studies showing that in 2011, nearly 45% of

Europeans had some degree of iodine deficiency (17). Due to this, the World Health Organisation (WHO) advocates a daily iodine intake for pregnant women of 250 µg daily, with ATA recommending a 150 µg daily supplementation in the form of potassium iodide for women who are pregnant, lactating or planning a pregnancy with the objective of maintain an adequate iodine level (2,10) Worldwide, strategies varies by region and local dietary intake in order to meet iodine requirement in pregnant and lactating women (2). The only way to verify if an adequate intake is been made is trough measurement of median urine iodine concentration, although this cannot be considerate as a marker for individual iodine status (9).

Screening for thyroid disease

The latest advances in the understanding of the pathophysiology of the thyroid gland during pregnancy and the adverse impact it can have in the mother and the foetus led to a vigorous scientific debate on the advisability of universal thyroid screening in early pregnancy or pre-pregnancy status comparing to case find approach (57). Important to notice is that SCH, excluding euthyroid women who are TPOAb positive, is the most common thyroid disorder during pregnancy and any consideration related of thyroid screening depend on the impact and the potential benefits of treating SCH (19).

The first step for this discussion was to evaluate thyroid disorders according to Wilson and Jungner criteria (**Table III**), that can tell us that TSH has the potential to be a good screening teste provided it improves offspring health (20). Another argument used to universal screening is that the latest clinical practice guidelines published by the biggest associations provide persuasive arguments for early detection and treatment of OH and SCH to prevent negative outcomes during pregnancy and this tactic only can be enplane with an universal screening approach (9,56). Besides this, three studies have evaluated whatever universal screening is cost-effective, with all three showing that it is cost-effective and would remain cost-effective even when they assumed no benefit for treatment of SCH (57). It is too important to notice that most of the routine analyses done in the first trimester of pregnancy deal with medical conditions less prevalent that SCH and are preformed simply to clinical inertia (19).

Table III – Wilson and Jungner criteria applied to TSH

Criteria	Application to thyroid screening	Ref.
- *The condition should be an important health problem*	SCH has a high prevalence	(14)
- *The natural history of the condition should be adequately understood*	Annual rate of progression from SCH to OH was 2.6% in negative thyroid antibodies women and 4.3% in positive ones	(20)
- *There should be a recognized latent or early stage*	SCH precedes the development of OH	(12)
- *There should be an accepted treatment for patients in early stage*	Thyroid function is especially important in the neurodevelopment of the foetus in the first 9-12 weeks of pregnancy	(58)
- *There should be a suitable test or examination*	TSH is the gold standard examination for the early diagnose of SCH	(3)
- *The test should be acceptable*	TSH is a simple blood test	(20)
- *Intervals for repeating the test should be determinate*	Usual guidance is estipulate in ATA and ETA guidelines	(10,11)
- *Facilities for diagnosis and treatment should be available*	Thyroxine replacement is a simple treatment that any patient can do by itself	(56)
- *The risks should be less that the benefits*	The risks of taking a blood teste are minimal and other types of screening are already done in the same time	(19)
- *It should be cost-effective*	Three previous studies have proven that universal-screening is cost-effective	(57)

The biggest argument against universal screening is the lack of an effective treatment to the most prevalent disorder, the SCH., in an effective way (59). Negro et al. performed a study with 4562 comparing case-finding and universal-screening approach concluding that universal-screening compared with case-finding did not result in a decrease in adverse outcomes (57). Hereupon, ATA and ETA keep recommending a case-finding approach to screening (56). Risk factor for target criteria for SCH are exposed in **Table IV** (20). Reasons to define this case-finding screening are well known and are related to the specific practicalities that cannot be underestimated to asses thyroid function in pregnant women, including trimester and population specific ranges that are difficult to achieve everywhere and to the uncertainty about we being able to reduce the negative outcomes that SCH can cause on pregnancy to the women and the foetus (7,56). In 2012, a survey was performed by the ETA were clinicals

reported how they use to approach this screening problem: 42% of respondents reported that they routinely chose an universal screening approach, 43% performed case-finding screening (35).

Table IV – SCH risk factors for target case-finding screening

SCH Risk Factors
Age > 30 years
Personal history of thyroid disfunction
Prior head or neck irradiation
Prior thyroid surgery
Family history
Symptoms
Presence of goitre
TPOAb positivity
Autoimmunity of other origin
Infertility
History of miscarriage or preterm delivery
Iodine deficient area
Medication and iodinated contrast media
Morbid obesity (BMI > 40kg/m^2)

In resume, SCH on pregnancy is considered an health problem and can cause a lot of negative outcomes (14,18). The question if we should or not treat SCH to establish normal ranges of TSH levels in pregnant women remains a question, but the paradox is that whilst a lot of search is been made to answer this, clinicals are increasingly using levothyroxine, in some way in an empirical use (56). The objective of this work is to make a systematic review to understand how to manage SCH and if we have or not an efficient available treatment, in order to start an efficient global approach and define the best strategy for screening.

METHODS

A systematic review of the literature was performed with app types of articles found in a certified medical database – PubMed. The search was performed on August 23rd, 2018 and the following search words were used: “pregnancy”, “subclinical hypothyroidism”, “treatment”. From this search 225 articles were obtained.

From these 225 articles, 69 were excluded as they were published before January 2010; 39 were excluded as they were studies in other species besides humans; 6 were excluded as they didn’t study female genre; 19 were excluded as they were not written in English, Portuguese or Spanish; 5 were excluded as they studied specifically and only cases of infertility; 7 were excluded since they did not referred in any part the pregnancy status; 11 were excluded as they studied specifically and only women going through methods of assisted reproductive technology (ART); 10 were excluded as they studied a very specific and small population not being representative enough; 5 were excluded as they didn’t mentioned SCH in any part of the articles; 8 were not used as they had no new information. After preforming this selection 47 articles were selected.

From the 55 articles selected, 21 were original articles of clinical research, 32 were state of the art systematic reviews and metanalyses and 2 were case study articles.

Besides this, it was performed a research of the last clinical practice guidelines about the theme and were selected the ATA 2017 (10) and ETA 2014 (11) guidelines due to the different point of views they show in some of the subjects related to SCH.

After reviewing all the bibliography found it was decided to add 16 more studies (24,25,51–53,55,60,61,26,28,30,31,33,45,47,49) that were referred on the already selected articles due to their relevance to the work.

RESULTS

Levothyroxine

Synthetic levothyroxine (LT4) is a levo-isomer of thyroxine with the same biochemical activity as the endogenous hormone and is the actual and only known recommended treatment for gestational hypothyroidism (35). It is recommended to treat patients in a non-pregnant status with SCH with: musculoskeletal symptoms, progression to OH, coronary heart disease, neuropsychiatric symptoms and other miscellaneous (12).

LT4 is proven to be safe during pregnancy and breastfeeding and carries no risk to the foetus and in the offspring. The drug is taken by oral ingestion, approximately 80% is absorbed in the gastrointestinal tract with a peak serum concentration obtained in about 2-4 hours after ingestion (35). In the serum, LT4 similarly to T4, is bound to TBG, thyroxine binding pre-albumin and albumin (41). LT4 is mainly metabolised in the liver through de-iodination and its excretion is made in the kidneys (35). A huge number of factors may led to a reduction in LT4 availability such as malabsorption, ingestion with some types of food and beverages, and pharmacological interactions (62). Therefore, LT4 should be taken with water, first thing in the morning and should not be taken with any other medication or food (35).

Although LT4 is safe in pregnancy, with just a few reported adverse effects such as tachyarrhythmias, angina pectoris and low bone mass, we should considerate the risk of overtreatment (12,35). In the Controlled Antenatal Thyroid Screening study (CATS) 10% of women going through LT4 treatment for hypothyroidism required dose reduction based on low TSH and high FT4 concentrations and some side effects such as palpitations (60). In other study performed in women treated with LT4, 13.6% were overtreated with 5.1% having TSH levels <0.1 mU/L, but it was concluded that this transient suppression was not associated with increase on negative outcomes (35). However, a population-based prospective cohort studied the association of maternal thyroid hormone levels with child's IQ and brain morphology with a sample of 3839 mother child pairs, concluded that high maternal FT4 concentrations during pregnancy are associated with lower IQ and low grey matter and cortex volume in the offspring, suggesting that LT4 therapy for SCH during pregnancy, with the aim of achieving high-normal TSH levels, carry the potential risk of adverse child neurodevelopment outcomes (40). The high free LT4 concentrations in pregnant women have also been linked to new-borns small for the gestational age and with LBW (56).

The major adversity about LT4 therapy on pregnant women is the absence of data on concentration of LT4 in the foetus, having no markers to monitor the utero-placental passage of LT4 (63). However, a study published by *Spremovic-Radjenovic et al.* showed that FT4 concentrations are higher than normal ranges in about 60% of foetus from euthyroid mothers

who had received LT4 therapy, studying this concentrations from blood samples of the foetus obtained by cordocentesis (56).

Studies against treatment

Two major trials were performed in order to understand if LT4 treatment would be beneficial to women with SCH and concluded that there no vantage in using LT4 to reduce the risk of negative outcomes in the mother or the foetus (56). In the CATS study, by *Lazarus et al.*, there was no difference in the gestational age at delivery or in the infant birthweight. (60) In a study published by *Casey et al.* treatment for SCH did not result in better cognitive outcomes in the child 5 years after birth (23). One important thing to notice in those two studies is therapy started in a gestational age that may be considered late, 13 and 8-20 respectively, especially to study neurodevelopment outcomes (4).

In addition, other smaller studies have been published that show similar results (4). In three different studies, *Yan et al.* and *Negro et al.* have studied the effects of LT4 therapy in TPOAb positive women with recurrent miscarriage finding no improvement on birth rates (24,25). *Lata et al.* have studied both women with SCH and TPOAb positive and found no difference in miscarriage rate on the ones treated with LT4 (26). *Bernardi et al.* published a prospective non-randomised study in women with SCH and history of recurrent early pregnancy loss treated with LT4 and no significant differences were found in live birth rates either (27). In **Table V** we can find a summary of this studies.

Table V – Studies against LT4 treatment on pregnancy

Study	Population	Outcome measured	Results	Ref.
Bernardi et al.	39 women with SCH (TSH>2.5mU/L), 24 going through LT4 treatment	early pregnancy loss	No benefits found on LT4 therapy on early pregnancy loss rate	(27)
Casey et al.	667 women with SCH (TSH>3.99mU/L), 339 going through LT4 treatment	child IQ in the offspring	No benefits found to LT4 therapy on child IQ	(23)
Lata et al.	100 women, 27 women with SCH (TSH>4.2 mU/L) and 31 TPOAb positive	Miscarriage	No benefits found on LT4 therapy on miscarriage rates	(26)

	going through LT4 treatment			
Lazarus et al.	986 women with SCH (TSH>4.2 mU/L), 494 going through LT4 treatment	pregnancy outcomes, child IQ in the offspring	No benefits found on pregnancy outcomes or child IQ	(60)
Negro et al.	393 TPOAb positive women, 198 going through LT4 treatment	Miscarriage, Preterm delivery	No benefits found on LT4 therapy on miscarriage and pre-term delivery	(25)
Yan et al.	34 women TPOAb positive with current miscarriage, 17 going through LT4 treatment	live birth rate	No benefits found on live birth rate	(24)

Studies in favour of treatment

Over the last few years studies have been published showing benefits on treating pregnant women with SCH with LT4. *Negro et al.* published a large-scale study showing that treatment of SCH, even when identified by a case-finding screening approach, is associated with a lower risk of negative outcomes (28). *Ma et al.* published a prospective non-randomised study showing controversial results with LT4 treatment lowering the risk of miscarriage and foetal macrosomia but raising the risk for caesarean delivery (21). *Maraka et al.* have published two different retrospective studies showing lower risk of LBW and Apgar score, and low risk of pregnancy loss in women with SCH receiving LT4 treatment, but with some controversial findings showing a high risk of preterm delivery, gestational diabetes and pre-eclampsia in those same women (29,30). Two metanalysis published by *Reid et al. and Velkeniers et al.* have shown similar results concluding that LT4 treatment can lower the risk of miscarriage and preterm delivery, with *Maraka et al.* reporting no effects on lowering the risk for pre-eclampsia (22,31). Another large-scale study was performed by *Nazarpour et al.* concluded that using the TSH cut off >4.0 mU/L LT4 therapy can decrease the risk of preterm delivery (32).

Smaller recent studies have also been published showing similar results. *Abalovich et al.* published a study showing that the outcomes in pregnancy were not dependent on whether the hypothyroidism is OH or SCH but on the treatment received (33). *Ju et al.* published a

study concluding that the overall risk of negative outcomes during pregnancy in women with SCH is lower in LT4 treated women than in the no treated ones (34).

On **Table VI** there is a summary on these articles.

Table VI – Studies in favour of SCH treatment on pregnancy

Study	**Population**	**Outcome measured**	**Results**	**Ref.**
Abalovich et al.	150 women, 21 with SCH (TSH>5mU/L) going through LT4 treatment	Abortion, Preterm delivery	↓ abortion ↓ preterm delivery	(33)
Ju et al.	457 women, 184 with SCH (TSH>97.5th percentile) going through LT4 treatment	PROM, Foetal macrossomia, Gestational diabetes, Hypertensive disorders, Postpartum haemorrhage, Preterm labour, Oligohydramnios, Foetal distress, LBW	↓ PROM ↓ Foetal macrosomia ↓ Gestational diabetes ↓ Hypertensive disorders ↓Postpartum haemorrhage ↓ Preterm labour ↓ Oligohydramnios ↓ Foetal distress ↓ LBW	(34)
Ma et al.	1671 women, 105 with SCH (TSH>2.5mU/L) going through LT4 treatment	Miscarriage, Foetal macrosomia, Caesarean delivery	↓ Miscarriage rate ↓ Foetal macrosomia ↑ Caesarean delivery	(21)
Maraka et al.	366 women, 82 with SCH (TSH>2.5mU/L) going through LT4 treatment	LBW, Low Apgar score, Gestational hypertension, PROM, Pregnancy loss,	↓ LBW ↓ Low Apgar score =Gestational hypertension = PROM = Pregnancy loss	(29)

		Preterm delivery, Gestational diabetes, Pre-eclampsia	= Preterm delivery = Gestational diabetes = Pre-eclampsia	
Maraka et al.	5404 women, 843 with SCH (TSH>2.5mU/L) going through LT4 treatment	Pregnancy loss, Preterm delivery, Gestational diabetes, Pre-eclampsia	↓ Pregnancy loss ↑ Preterm delivery ↑ Gestational diabetes ↑ Pre-eclampsia	(30)
Nazarpour et al.	1458 women, 366 with SCH (TSH>2.5mU/L) going through LT4 treatment	Preterm delivery	↓ Preterm delivery	(32)
Negro et al.	4562 women, 117 with OH or SCH (TSH>2.5mU/L) going through LT4 treatment	Miscarriage, Low IQ on the offspring, Visual-motor deficiencies on the offspring, Preterm deliver, Postpartum thyroiditis	↓ Miscarriage ↓ Low IQ on the offspring ↓Visual-motor deficiencies on the offspring ↓ Preterm delivery ↓ Postpartum thyroiditis	(28)
Reid et al.	535 women with OH or SCH (TSH>4mU/L) going through LT4 treatment	Preterm delivery, Pre-eclampsia,	↓ Preterm delivery = Pre-eclampsia	(22)
Velkeniers et al.	220 women with SCH (TSH>4.0mU/L) going through LT4 treatment	Preterm delivery, Miscarriage	↓ Preterm delivery ↓ Miscarriage	(31)

Management and Doses

The main goal for LT4 treatment of pregnant women with SCH is to achieve target TSH levels below the pregnancy-specific population-based references (62). In the cases that SCH is found and treated before conception, studies indicate that adequate preconception replacement should be provide and an empirical increase should be made to the preconception doses since, in addition to the physiological changes in thyroid during pregnancy, the gastrointestinal absorption is altered on pregnant women (4). *Abalovich et al.* and *Wang at al.* have published results showing that starting preconception or in early pregnancy treatment can reduce the risk for miscarriage and preterm delivery (33,50). Three different populational studies from United Kingdom, United States of America and Italy have shown that the vast majority of pregnant women with previous hypothyroidism needed an increase on the pre-conceptional dosage (4). It is estimated that the thyroid gland has to increase its hormonal produce in about 30-50% during pregnancy, so it is considerate that pregnant women who are already treated with LT4 could achieved an euthyroid state by doubling the usual dose on two days each week starting on the day they have a positive pregnancy test (4,17). On the order hand, there are some observational studies suggesting that a lot of women with pre-conceptional TSH levels below 1.2mU/L will be able to maintain the levels despites no dosage adjustment (62).

For women diagnosed with SCH during pregnancy and for those already treated, the procedures that should be used, in order to manage the treatment seems to be well defined (4,17,35). Regular thyroid function monitoring should be performed to keep the levels on the ideal range and women should preform thyroid function tests monthly during the first 20 weeks of gestation. After this, two more tests should be performed, one in the beginning of the third trimester and another in the mid-third trimester. A properly increase or decrease should be made to the daily dose in order to achieve the levels below the reference range and an additional thyroid hormone test should be performed 4 weeks after any adjustment (4). After delivery, in women that started the LT4 treatment during pregnancy, LT4 should be stopped in 2 weeks, and in women going through previous treatment, the pre-conceptional dose should be established. In all the cases thyroid function should be tested 6-8 weeks postpartum (4). In a study of five-years follow-up for women with SCH in pregnancy going through LT4 treatment, *Beverley et al.* conclude that the vast majority of cases of SCH during pregnancy are transient and women will not need any LT4 treatment after delivery (36). In the same study they conclude that the percentage of women that had the need to maintain LT4 therapy were TPOAb positive, being this the major risk factor for women in the postpartum (36).

On terms of dosage that should be established for pregnant women recently diagnosed with SCH, studies keep showing some different results. *Abalovich et al.* published a study concluding that an approximately dose off 88µg/day would be the optimal dosage to obtain

euthyroidism in 90% of women during all pregnancy, with some variation depending on the TSH level before treatment (37). *Penin et al.* published two different studies trying to achieve the best results with the first one showing that an initial dose of 50µg/day will be enough to obtain TSH levels between 0.3-4.5 mU/L in 80% of women and with the second one concluding that a dose of 75µg/day will be optimal in order to obtain TSH levels between 0.3-4.5 mU/L in almost 100% of women (38,39). Other two studies worth mentioning are *Lazarus et al.* concluding that the median LT4 dose used to achieve euthyroidism in 85% of women was 150µg/day and *Ross et al.* recommending a weight based dosage of 1µg/kg/day (37,39).

Clinical Practice Guidelines

ATA guidelines, published in 2017, recommend first the evaluation of TPOAb status. After this, should be recommended LT4 therapy for women with TSH greater than the pregnancy-specific population-based reference range or, when this references are not available, TSH>4mU/L and TPOAb positivity (10). Besides this, ATA recommends that treatment may start around week 9 of pregnancy with a daily doses of 50µg (10). On **Table VII** there is a summary of ATA guidelines recommendation.

Table VII – ATA guidelines for treatment of SCH in pregnancy

TSH level	TPOAb status	Level of recommendation
Recommend		
>pregnancy-specific reference range	+	Strong recommendation, moderate-quality evidence
>10.0 mU/L	-	Strong recommendation, low-quality evidence
Considered		
>2.5 mU/L but < pregnancy-specific reference range	+	Weak recommendation, moderate-quality evidence
>pregnancy-specific reference range but <10.0 mU/L	-	Weak recommendation, low-quality evidence
Not recommend		
within the pregnancy-specific reference range or <4.0 mU/L if unavailable	-	Strong recommendation, high-quality evidence

ETA 2014 guidelines recommend treatment of all women with TSH> to the pregnancy-specific reference range or >2.5 mU/L if unavailable, with the goal of normalize TSH values. In the

newly diagnosed patients it is advised to use an initial daily dose of 1.20µg/kg. Those women with pre-pregnancy treated SCH should do an increase of 25 to 50% in daily doses to ensure TSH<2.5mU/L and after delivery it is recommended the reduction of the dose to the preconception one. When SCH is diagnosed during pregnancy and if TSH<5.0mU/L with TPOAb negative treatment should be interrupt and TSH levels checked 6 weeks later. Women with SCH during pregnancy should be re-evaluated 6 months and 1 year after delivery to check the need for LT4 treatment (11).

CONCLUSION

After the analysis of the published studies results, it can be concluded that the majority of the studies around management and treatment of SCH during pregnancy showed that it is beneficial to use LT4 in order to obtain reference range TSH levels, especially in order to reduce the risk of miscarriage and preterm delivery (21,22,34,25,26,28–33). Analyzing other outcomes, it can be concluded that results are controversial about pregnancy loss (24,29,30) and they show that there is no benefit on treating SCH during pregnancy in order to improve the child IQ in the offspring (23,28,60). LT4 treatment can too be useful to reduce the risk of foetal macrosomia and LBW but more studies are needed in order to confirm this results (21,29,34). There are some controversial results that can show that LT4 treatment decreases the risk for gestational diabetes and pre-eclampsia and other hypertensive disorders during pregnancy. (30,34). Benefits on reducing outcomes like PROM, postpartum haemorrhage, oligohydramnios, foetal distress, low Apgar score, visual-motor deficiencies on the offspring and postpartum thyroiditis cannot be considerate since they are mentioned only once on all the observed studies (28,29,34), the same applies to the study showing an increase in caesarean delivery among pregnant women going throught LT4 treatment (21).

Other object we must considerate are the different cut-offs used in all studies to define SCH that can lead to a wrong analysis of the results. This came to support the need to define population-based reference range TSH levels. Hereupon, every country must have clinical practice guidelines with studies made with its own population.

When discussing the most recommended dose the physician should opt for one of the mentioned on clinical practice guidelines and perform the recommended thyroid hormone evaluation in order to do dose adjustment to avoid TSH levels out the reference ranges (10,11).

With this results it can be concluded that clinical practice guidelines already published (10,11) should be taken in consideration and used to manage SCH during pregnancy, always having present the risk for overtreatment and not forgetting the medical bioethicist principal of non-maleficence. In order to perform the best medical practice, it is important to discuss with the patient the possible risks and benefits of therapy and the decision should be taken based on both medical and patient opinion and believes.

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