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TELMA CID LOPES MORENO

Hypothyroidism and Pregnancy: Debate Over the New Guidelines

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PROFESSOR DOUTOR MIGUEL MELO

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HYPOTHYROIDISM AND PREGNANCY: DEBATE OVER THE NEW GUIDELINES

Telma Cid Lopes Moreno

Miguel Melo

Endereço de correio eletrónico: telmaclm@gmail.com

CONTENTS

ABSTRACT

Pregnancy can be considered as a stress test for thyroid function, as the demands on thyroid hormone production increase approximately 50%, to ensure adequate levels for fetal somatic growth and neurodevelopment. In healthy pregnant women, these physiological changes present no challenge, but thyroid dysfunction is common in pregnancy. Hypothyroidism is the most common presentation of thyroid disease during pregnancy, with a prevalence of 0.2% to 0.6% of overt hypothyroidism and 3.5% to 18% of subclinical hypothyroidism, both being associated with adverse effects on pregnancy outcomes and child development. A relationship between hypothyroidism and thyroid autoimmune disease is well established and the latter is common in women of child-bearing age. Despite the potential dangers of thyroid malfunction in pregnancy, it is still controversial whether all pregnant women should be evaluated for thyroid function, since it is not clear that treatment could prevent these negative outcomes, particularly in subclinical hypothyroidism and thyroid autoimmunity. In 2011, the American Thyroid Association released its first guidelines on the diagnosis and management of thyroid disease during pregnancy and postpartum, which have been revised in the year of 2017. This Review aims to understand the reasons for the reformulation of some clinical recommendations and to revise hypothyroidism in pregnancy, from its causes to possible adverse outcomes, as well as screening and management.

KEYWORDS

Hypothyroidism, pregnancy, iodine, autoimmunity, thyroxine, screening, management, guidelines

RESUMO

A gravidez pode ser considerada um teste de *stress* para a tiróide, uma vez que a necessidade da produção de hormonas tiroideias aumenta em cerca de 50%, de modo a assegurar níveis hormonais adequados para o crescimento somático e neurodesenvolvimento do feto. Em mulheres grávidas saudáveis, estas alterações fisiológicas não constituem um desafio adicional para a tiróide mas a disfunção tiroideia é comum durante a gravidez. O hipotiroidismo é a manifestação mais comum de doença tiroideia durante a gravidez, com uma prevalência de 0,2% - 0,6% de hipotiroidismo clínico e de 3,5% - 18% de hipotiroidismo subclínico, estando ambos associados a efeitos adversos na gravidez e no desenvolvimento da criança. A relação entre hipotiroidismo e doença auto-imune da tiróide está bem estabelecida e, esta última, é comum em mulheres em idade fértil. Apesar dos potenciais perigos de disfunção tiroideia na gravidez, continua a ser controverso se a função tiroideia deveria ser avaliada em todas as mulheres grávidas, uma vez que não é claro que o tratamento possa prevenir estes efeitos adversos, particularmente nos casos de hipotiroidismo subclínico e doença auto-imune da tiróide. Em 2011, a *American Thyroid Association* publicou as suas primeiras *guidelines* sobre o diagnóstico e seguimento de doença tiroideia durante a gravidez e o período pós-parto, que foram revistas no ano de 2017. Este Artigo de Revisão pretende compreender a razão da reformulação de algumas das recomendações prévias e, ao mesmo tempo, rever o hipotiroidismo na gravidez, desde as suas causas até aos possíveis efeitos adversos, assim como o seu diagnóstico e tratamento.

PALAVRAS – CHAVE

Hipotiroidismo, gravidez, iodo, auto-imunidade, levotiroxina, rastreio, seguimento, guidelines

INTRODUCTION

Pregnancy has a deep impact on maternal thyroid function. Production of thyroid hormones during pregnancy should increase by nearly 50%, as they are essential for the normal development of the fetus (1). In healthy women, it is possible to maintain an euthyroid state during pregnancy, even with increased demands for thyroid hormone production, but 2 – 5% will suffer from gestational hypothyroidism (2).

Hypothyroidism is biochemically defined as a thyroid-stimulating hormone (TSH) concentration elevated beyond the upper limit of the pregnancy-specific reference range. It can be further divided into overt hypothyroidism, which combines an elevated TSH with a decreased free thyroxine (FT4) concentration, or subclinical hypothyroidism, in which TSH is elevated but FT4 is within the normal trimester-specific range (3). Overt maternal hypothyroidism accounts for 0.2% to 0.6% of all cases of hypothyroidism in pregnant women, whereas subclinical hypothyroidism is more prevalent, affecting 3.5% to 18% of all pregnancies, depending on the upper limit of the TSH reference range (4). Thyroid autoimmunity, in the form of thyroid peroxidase (TPOAb) and/or thyroglobulin antibodies (TgAb), is associated with a higher risk for development of thyroid dysfunction during pregnancy, with thyroid auto-antibodies being detected in up to 18% of all pregnant women (5).

Nowadays, the association between overt thyroid dysfunction and negative pregnancy outcomes is well established and includes pregnancy complications, as well as adverse effects on the child neurodevelopment. Still, the question remains whether all pregnant women should be evaluated for thyroid function before or during pregnancy, since the impact of treatment on improving health outcomes is not clearly established, especially in subclinical thyroid disease and thyroid autoimmune disease (6).

Hoping to shed a light on the management of thyroid dysfunction during pregnancy, the American Thyroid Association (ATA) released its first guidelines in 2011, and this document was revised in 2017. This Review Article aims to understand the reasons behind the reformulation of some clinical recommendations over this six-year period, as well as to revise the current knowledge on physiology of thyroid hormones during pregnancy, causes of maternal hypothyroidism and its effects on pregnancy outcomes and the screening and management of thyroid disease during pregnancy.

METHODS

During September 2017, a literature search in PubMed for articles in English from the year 1994 to 2017 (search terms included: thyroid physiology, thyroid function, pregnancy, overt hypothyroidism, subclinical hypothyroidism, hypothyroxinemia, thyroid autoimmunity, iodine deficiency, iodine status, adverse pregnancy outcomes, screening for thyroid dysfunction, treatment of hypothyroidism, ATA guidelines) was conducted. A web page referring to an on-going clinical trial, accessed on September 15th 2017, was also consulted. The search was repeated in January 2018 using the same search terms and an article from 2018 was included. Approximately 135 articles were reviewed and, of these, 87 were included in this Review. The remaining articles were excluded for not being relevant to the main subject of this Review or due to repetitive information.

RESULTS

THYROID PHYSIOLOGY AND THYROID FUNCTION TESTING IN PREGNANCY

Normal pregnancy is associated with several hormonal and metabolic changes, starting with an increased demand for thyroid hormone production by 50%, in order to maintain a euthyroid state throughout pregnancy. Total T4 concentrations increase significantly in the first half of gestation, reaching a peak around week 16 and then a plateau until delivery. This is directly related to the also increased production of a thyroid hormone transport protein, the thyroid binding globulin (TBG) protein, due to high levels of circulating estrogens. It is estimated that there is a 2,5- to 3-fold rise in TBG values during pregnancy when compared to basal levels. Conversely to the total thyroid hormone increase, most studies report a slight decrease in FT4 concentrations during pregnancy, with lower FT4 values in pregnant women by an average 10% - 15% compared to non-pregnant women. In most women, however, these values are maintained within the non-pregnant reference range. From the first weeks of gestation, the placenta produces human chorionic gonadotropin (hCG), reaching its highest levels around week 10. This hormone exerts a direct stimulatory effect in the TSH receptor, because of the structural homology between the hCG and TSH molecules, which leads to increased thyroid hormone production and, in turn, a decreased TSH concentration during the first trimester of pregnancy (1, 7, 8).

Another event concerning the metabolic changes of pregnancy is the peripheral metabolism of thyroid hormones. There are three different enzymes responsible for deiodination of thyroid hormones; however, only type 2 (D2) and type 3 (D3) deiodinases' activities undergo more significant alterations during pregnancy. D2 is an

activating enzyme mostly present in the brain, pituitary gland, placenta and brown adipose tissue. In the placenta, it generates T3 to maintain an adequate local concentration of this hormone for a normal fetal tissue development. Nonetheless, in the placenta the predominant enzyme is D3 that converts T4 to the inactive form rT3, preventing the exposure of the fetus to an excess of maternal thyroid hormones and, at the same time, providing a source of iodide for fetal thyroid hormone production. For these reasons, the fetal circulating levels of T3 are relatively low whereas fetal brain concentration of T3 reaches 60% - 80% of that of an adult (1, 9).

Pregnancy is further associated with an increase in renal blood flow and glomerular filtration that are responsible for a higher renal iodine excretion that constitutes a source of iodine loss. The increased demand for thyroid hormone production contributes even more for the tendency to the reduction of the maternal iodide pool, as so does the transference of some of the available iodine from the mother to the fetus through the placenta, given that around mid-gestation the fetal gland can already produce its own thyroid hormones (7, 10). For healthy pregnant women with adequate iodine storage preconception, the thyroid will have a physiological adaptation to the pregnant state but, in cases of previous inadequate iodine intake, pathological changes will occur with consequences both on the mother and the fetus. The latter will be discussed further ahead in this review.

Given these pregnancy-related thyroid changes, it is important to establish normal reference ranges for thyroid function in each trimester of pregnancy. As previously explained, TSH concentrations decrease in the first trimester and then gradually rise in the second and third trimesters even though both the lower and upper limits of TSH values are lower than in the non-pregnant population by about 0.1 - 0.2 mU/L and 0.5 - 1.0 mU/L, respectively (5, 8). In the 2011 ATA guidelines, the upper

reference limit for TSH concentration was 2.5 mU/L in the first trimester and then 3.0 mU/L in the second and third trimesters. Six years later, the 2017 ATA guidelines state that "an upper reference limit of ≈ 4.0 mU/L may be used". Indeed, several studies published more recently, show that the 2011 guidelines' TSH cut-offs are considerably lower than those calculated by population-based reference ranges (4). A study in Chinese pregnant women aiming to establish a TSH reference range for the diagnosis of subclinical hypothyroidism revealed an upper limit for TSH concentrations in the first trimester much higher than the fixed 2.5 mU/L, reporting TSH reference intervals of 0.14 – 4.87 mU/L in the first trimester (11), which means that using the proposed upper limits could result in overdiagnosis of thyroid dysfunction. Similarly, in two different Danish studies "an upper TSH reference limit as low as 2.5 mU/L was not observed in any week of early pregnancy" (12) and "when applying the ATA-guideline range for TSH, a mean of 1.9% (up to 4.0%) in cohort 1 and 4.2% (up to 8.2%) in cohort 2 had abnormal TSH-values, despite the fact that these women were within the limits of their own cohort-specific reference range" (13). These data reinforce the recommendations to use preferentially population- and trimester-specific reference ranges for serum TSH during pregnancy (3, 5) to avoid misclassification and overdiagnosis of gestational thyroid disease.

Even though the reduction in TSH reference ranges during pregnancy is practically universal, the extent of this reduction varies significantly depending on some factors, one of them being ethnicity. Ethnic differences may be explained by genetic, dietary, environmental and cultural factors (4) and can influence the diagnosis of thyroid disease. A study in which ethnicity-specific reference ranges, instead of the total population reference ranges, were used changed the diagnosis in 18% of the women who initially were classified as having abnormal test results (14). In this study, the

pregnant women were from four different ethnic backgrounds, Dutch, Moroccan, Turkish and Surinamese, and the results showed that Turkish and Moroccan women had a higher risk of elevated TSH values compared to the Dutch and the Surinamese populations. Another determinant factor of thyroid function during pregnancy is the Body Mass Index (BMI). On the other hand, thyroid dysfunction itself can also adversely affect maternal weight with a higher risk of hypertensive disorders, gestational diabetes, stillbirth and large size for gestational age infants in obese women. A prospective cohort study examined the associations of maternal TSH and FT4 levels with maternal pre-pregnancy BMI and gestational weight gain and found that higher TSH levels and lower FT4 levels were associated with a higher pre-pregnancy BMI and a higher risk of excessive gestational weight gain (15). Another study involving 1035 women also showed similar results with a significant correlation between higher BMI and lower FT4 levels, even though there was no correlation between BMI and TSH levels (16). Other risk factors for thyroid dysfunction include thyroid autoimmunity, iodine status, maternal age, smoking history and parity. As shown in a study by Korevaar *et al.*, maternal age (from 30 years onwards), parity and smoking are associated with a higher risk of decreased FT4 levels, even though higher parity and smoking are associated with a lower risk of both positivity for antibodies and high TSH levels (17). Nevertheless, the authors concluded that the identified clinical risk factors lacked proper discriminative ability and, therefore, did not accurately predict the risk of thyroid dysfunction. Recently, it was evaluated whether hCG, playing an important role in thyroid function in early pregnancy, could also be a risk factor for thyroid disease. Higher levels of hCG were associated with a lower risk of hypothyroxinemia and a higher risk of hyperthyroidism, but no association was found between hCG concentrations and the risk for overt or subclinical hypothyroidism. The study suggested

a lack of response to hCG thyroidal stimulation in women with subclinical hypothyroidism because, in these women, high hCG concentrations were not associated with higher FT4 levels (18). Furthermore, other risk factors for thyroid dysfunction mentioned above, such as a higher BMI and parity, were found to be associated with a lower response of the thyroid gland to hCG stimulation and thyroid autoimmunity severely impaired this response (19). Apart from the production of hCG, the placenta also produces angiogenic factors such as placental growth factor (PlGF) and soluble FMS-like tyrosine kinase-1 (sFlt1). PlGF is a proangiogenic factor, while sFlt1 acts as an antagonist of VEGF and PlGF signaling; both are important for the maintenance of pregnancy and fetal development. Being angiogenic factors, it was hypothesized that they could have a direct action on the maternal thyroid gland by affecting its vascularity and perfusion (20). It was shown that higher levels of sFlt1 were associated with decreased FT4 levels and an increased risk of hypothyroxinemia. Similarly, increasing levels of PlGF had the same effects and were also associated with lower TSH values. On top of this, high levels of angiogenic factors may also lead to an altered thyroidal response to hCG stimulation. This suggests that high levels of circulating angiogenic factors may be a risk factor for the development of mild thyroid dysfunction.

To evaluate thyroid function properly, apart from TSH measurements, thyroid hormone assessment in the form of FT4 is also important. Both 2011 and 2017 ATA guidelines recommend that assay method-specific and trimester-specific reference ranges should be applied. FT4 immunoassays are the most currently used tests for FT4 determination, despite being prone to several bias factors of which the physiological changes in TBG and albumin during pregnancy are important interfering variables (8, 21). The 2017 ATA guidelines state that, despite the inter-assay differences, the FT4 immunoassays perform reasonably well. There are other more accurate methods to

measure free thyroid hormones based on the physical separation of the free from the protein-bound T4 by equilibrium dialysis or ultrafiltration, but these approaches are "time consuming, costly, and often impractical". Alternatively, a free thyroxine index or total T4 measurement adjusted for pregnancy can be used as reliable methods of estimating thyroid hormone status during pregnancy (5).

IODINE STATUS AND NUTRITION

Pregnant women require higher iodine intake to make up for the physiologic alterations that affect iodine metabolism in pregnancy, consisting of an increased thyroid hormone production, an increased renal iodine clearance, changes of the peripheral metabolism of maternal thyroid hormones and also fetal iodine requirements (10). Women with inadequate pre-pregnancy iodine ingestion may have pathological repercussions with progressive depletion of iodine stores due to the increased demands of thyroidal activity during pregnancy (7, 10). Iodine deprivation will result in hypothyroxinemia, since iodine is necessary for thyroid hormone synthesis, meaning that total T4 production will decrease as well as free thyroid hormones. Assessment of iodine status of pregnant women can be done, according to the World Health Organization (WHO), using median urinary iodine concentrations (UIC): an UIC < 150 μg/l reveals an insufficient iodine intake, whereas an UIC 150 – 249 μg/l translates an adequate intake.

The consequences of iodine deficiency disorders depend on the time of occurrence and whether we are in the presence of severe or mild-to-moderate iodine deficiency. Severe iodine deficiency impairs thyroid hormone production that, in turn, stimulates an increased TSH production that acts as a goitrogenic stimulus both in the mother and the fetus. In fact, in iodine deficient areas, the thyroid volume can increase

by 20% to 35% during pregnancy and thyroid nodules can be present in up to 45% of pregnant women (22). Other effects of severe iodine restriction include increased risks of pregnancy loss, stillbirth, congenital anomalies and perinatal and infant mortality (23). Fetal brain development takes place over a long period of time, that goes from a few weeks post-conception to the first years after birth, and is highly dependent on adequate thyroid hormone levels (24). Thus, reduced thyroid hormone synthesis due to lack of proper iodine intake can lead to irreversible brain damage with mental retardation and neurological abnormalities in the form of cretinism (profound intellectual impairment, deaf-mutism and motor spasticity), the most severe manifestation of iodine deficiency (25-27). As a matter of fact, WHO considers iodine deficiency to be "the single most important preventable cause of brain damage" worldwide.

That severe iodine deficiency results in adverse outcomes on neurodevelopment is well established, however, less is known about the effects of mild-to-moderate deficiency on child cognition. A study in the United Kingdom evaluated the effects of maternal mild iodine deficiency on their children cognitive outcomes by assessing child IQ at age 8 years and reading ability at age 9 years (28). The results showed that a higher proportion of children born to women with an iodine-to-creatinine ratio < 150μg/d had suboptimum cognitive outcomes when compared to those born to women in the ≥ 150 μg/d group. Those children were more likely to have lower scores for verbal IQ, reading accuracy and reading comprehension. Mild-to-moderate iodine deficiency has also been associated with poorer psychomotor development (29) and attention deficit and hyperactivity disorders (ADHD) (30). Thus, mild-to-moderate maternal iodine deficiency can lead to impaired cognitive outcomes that, even though less severe, can have long lasting impacts in the affected child.

Programs of universal salt iodization have significantly improved iodine nutrition worldwide but thirty countries remain iodine deficient (31). In Europe, ⅔ of the countries with data on iodine intake in pregnant women have reported low iodine intake compatible with mild-to-moderate iodine deficiency (32). For instance, in Portugal, only 16,8% of pregnant women had adequate iodine intake (UIC > 150 μg/l) and 23,7% actually had UIC levels < 50 μg/l, pointing to an inadequate countrywide iodine supply during pregnancy (33). For the reasons previously stated, and in accordance with WHO, the guidelines recommend that all pregnant women should be supplemented with a daily iodine dose of 250 μg. Last but not least, excessive iodine consumption can be harmful as reported by a U-shaped relationship between iodine intake and the occurrence of thyroid disease (25). In fact, it has been suggested a higher prevalence of subclinical hypothyroidism and hypothyroxinemia, as well as a higher risk of thyroid autoimmunity with higher UIC values (34). Consequently, the 2017 ATA guidelines recommend that a daily iodine intake > 500 μg should be avoided.

THYROID AUTO-ANTIBODIES

In an unselected population of women, the prevalence of TPOAb or TgAb ranges from 6% to 20% which makes the presence of thyroid auto-antibodies common in women of childbearing age (6, 35). Most women who test positive for thyroid auto-antibodies are euthyroid, but they are an important risk factor for thyroid dysfunction during pregnancy (4). In fact, thyroid autoimmunity represents the main cause of hypothyroidism which will lead to poor obstetric outcomes and, even in women with normal thyroid function, thyroid auto-antibodies have been associated with adverse pregnancy outcomes. Even though the exact mechanisms through which thyroid autoimmunity influences obstetric outcomes are unknown, there are two main hypotheses that could explain this association (4, 35). One of them proposes that the

presence of thyroid auto-antibodies could lead to thyroid dysfunction through subtle deficiency of thyroid hormones or incapacity of adequately increasing thyroid hormone production during pregnancy. Alternatively, thyroid auto-antibodies could be a part of an underlying global autoimmune state with direct consequences on the maternal-fetal unit. Interestingly, TPOAb-positive women do display a severely impaired thyroidal response to hCG stimulation in early pregnancy compared to those who are TPOAb-negative (19) which could lead to a lower availability of thyroid hormones. Women who are TPOAb-positive also have higher TSH concentrations and lower FT4 levels than TPOAb-negative women and a substantially increased risk of developing (subclinical) hypothyroidism during pregnancy (36, 37). In a study by Negro *et al.* (38), TPOAb-positive euthyroid pregnant women had higher basal TSH values, even though still within the normal range, at the beginning of pregnancy compared with TPOAb-negative women. As gestation progressed, TSH levels increased and, at delivery, 19% of these women had a TSH value higher than the normal range. Given the increased risk of TSH elevation and impaired thyroid function during pregnancy in these women, the 2017 ATA guidelines recommend that euthyroid, thyroid-antibody positive women should have TSH concentration measured at the time of pregnancy confirmation and then every 4 weeks through mid-pregnancy. On the other hand, pre-pregnancy and early pregnancy screening for thyroid dysfunction, including thyroid autoimmunity, has been proposed but remains not widely accepted, as it is stated in the 2011 ATA guidelines, which confirm that "there is insufficient evidence to recommend for or against screening all women for thyroid antibodies in the first trimester of pregnancy".

Thyroid autoimmunity is associated with several adverse pregnancy outcomes, ranging from miscarriage to preterm delivery. Also, in antibody-positive women, subfertility occurs more often (39). Main causes of infertility include female factors,

male factors, combination of female and male factors and idiopathic forms. Immunological factors, in this case represented by thyroid antibodies, may negatively influence female fertility by affecting the reproductive processes of fertilization, implantation and placental development (40). Poppe *et al.* undertook a prospective study in 438 women with various causes of infertility with the objective of assessing the prevalence of thyroid autoimmunity in these women (41). The infertile group was divided into five categories according to the cause of infertility: endometriosis, ovulatory dysfunction, tubal disease, male cause and idiopathic. When all these causes were pooled, there was no significant difference of thyroid autoimmunity in infertile women. However, when analyzing only the female-factor infertility (endometriosis, ovulatory dysfunction and tubal disease), there was a significant higher prevalence of TPOAb compared to controls, 18% versus 8%, respectively. In addition, a higher prevalence of thyroid autoimmunity has been found in women with polycystic ovary syndrome, an important cause for female infertility (42). Miscarriage (or spontaneous pregnancy loss) is usually defined by the loss of a pregnancy before 20 weeks of gestation and affects up to one in five women who conceive, making it a very common complication in pregnancy (35). Recurrent pregnancy loss, defined as either two consecutive spontaneous losses or three or more spontaneous losses, affects approximately 5% of couples trying to conceive and several risk factors have been reported, including parental chromosome abnormalities, uterine anomalies, anti-phospholipid syndrome and endocrine dysfunction (43). In fact, the presence of thyroid antibodies is strongly associated with sporadic and recurrent miscarriage (35, 39, 43). A prospective cohort study in low-risk women for thyroid dysfunction, in an iodine-sufficient region, evaluating the association between subclinical hypothyroidism and thyroid autoimmunity in early pregnancy (at 4 to 8 weeks of gestation) with miscarriage

found that the presence of thyroid antibodies with normal TSH levels (isolated thyroid autoimmunity) was associated with a higher risk of miscarriage and also an earlier gestational age of miscarriage (44). Even though there is an unequivocal association between thyroid antibodies and the miscarriage rate, this does not imply causality as the underlying mechanisms for such an association remain unknown. Several hypotheses have been proposed and include an antibody-mediated subtle thyroid hypofunction, an underlying generalized autoimmune state that could contribute to a greater rejection rate of implantation or the fact that thyroid antibodies, by representing a risk factor for infertility, could delay pregnancy in these women to an older age which, by itself, constitutes a risk factor for pregnancy loss (40). The presence of thyroid antibodies is also associated with preterm delivery, defined as birth prior to 37 weeks of gestation, which is responsible for up to 85% of neonatal deaths and long-term disability in those who survive (6, 35, 39). In a systematic meta-analysis, the odds of preterm birth doubled in women with thyroid auto-antibodies (35). Although thyroid antibodies are consistently associated with preterm delivery, the underlying mechanisms of such relationship are not yet clear. As mentioned before, a recent study by Korevaar *et al.*, hypothesized that TPOAb-positivity could interfere with gestational thyroid stimulation by hCG and contribute to the risk of premature delivery (19). They reported that, overall, TPOAb-positivity was associated with a 1.7-fold higher risk of premature delivery. Also, TPOAb-positive women with an impaired FT4 response to hCG stimulation, that is, low FT4 concentration with high hCG levels, had a 2.2- to 2.8-fold higher risk of premature delivery. Another study investigating the association between thyroid antibody status in euthyroid women with adverse pregnancy outcomes, reported a higher incidence rate of premature rupture of the amniotic membranes but, interestingly not of preterm birth, and also a higher risk of low birth weight (45).

Regarding the effect of autoimmunity in other common pregnancy complications, the relationship between thyroid auto-antibodies and gestational diabetes mellitus has been investigated, with studies suggesting that the mechanism of gestational diabetes is likely to involve insulin resistance that could be induced by an increase of pro-inflammatory cytokines associated with thyroid autoimmunity linked to an autoimmune generalized condition (46). In this meta-analysis, the authors conclude that there is a significant, albeit not strong, association between thyroid antibodies and the risk of gestational diabetes and that this association is stronger in TPOAb-positive women with thyroid dysfunction than in TPOAb-positive euthyroid women. Similarly, data from a prospective cohort study in Greece showed a 4-fold increased risk for gestational diabetes in women with a combination of high TSH and thyroid autoimmunity. However, such an association was not found in euthyroid women with isolated thyroid antibodies (47). A systematic review (39) did not establish an association between thyroid antibodies with other late pregnancy complications such as pregnancy-induced hypertension, pre-eclampsia, placental abruption or cesarean sections nor with perinatal mortality.

Some studies have investigated the association between thyroid autoimmunity in pregnancy and child development. Li *et al.* reported lower intellectual and motor development scores on children at 25 - 30 months of age born to euthyroid women with elevated TPOAb titers (48). In the Generation R study, investigators examined whether elevated titers of TPOAb in early pregnancy increased the risk of cognitive impairment or problem behavior in pre-school children aged 2.5 - 3 years old (49). The authors concluded that elevated titers of TPOAb did not affect their verbal or nonverbal cognitive function, but thyroid antibodies were associated with externalizing problems in children, particularly, ADHD problems. In another study (50), maternal thyroid

antibodies were implicated with early developmental delays on their children's IQ, even though these cognitive deficits were transient rather than permanent. The same authors had previously established a relationship between maternal TPOAb elevation during the third trimester of pregnancy with sensorineural hearing loss in their children (51).

In the same manner that screening women early in pregnancy for thyroid auto-antibodies and thyroid dysfunction remains controversial, so does treating thyroid antibody-positive, euthyroid pregnant women because there is lack of evidence on effective treatment interventions. Two on-going trials, the Thyroid AntiBodies and LEvoThyroxine (TABLET) trial in the United Kingdom and the T4Life trial in the Netherlands, are examining the effect of LT4 treatment in euthyroid, TPOAb-positive women with a history of recurrent miscarriage to assess its effects on live birth rate (43, 52). Surely, their results will help to generate important data about the efficacy of LT4 treatment and contribute to standardization of health care regarding this subject. Meanwhile, a study by Negro *et al.* sought to determine whether LT4 treatment exerted beneficial effects on obstetrical complications in euthyroid women with thyroid autoimmunity (38). It was concluded that treatment with LT4 had a positive effect on reducing the rates of both miscarriage and preterm delivery compared to the group of non-treated TPOAb-positive women. These results were achieved by maintaining the treated TPOAb-positive women in a euthyroid state throughout gestation. A similar prospective study in Iranian, TPOAb-positive pregnant women divided them into two groups: group A was treated with LT4 and group B received no treatment (53). The administration of LT4 decreased the rates of preterm delivery and of neonatal hospital admissions. Interestingly, it was not demonstrated a positive effect of LT4 on miscarriage rates, but the authors attribute this result to the fact that LT4 was not administered in the early stages of pregnancy when miscarriage occurs more frequently

(64.3% of women had not started LT4 by the 8th week of gestation). Therefore, both previous studies indicate that timing of treatment initiation is critical, as euthyroxinemia is primarily important in early stages of pregnancy. Nevertheless, the 2011 ATA guidelines expressed that there was not sufficient evidence to recommend for or against LT4 treatment in thyroid antibody-positive, euthyroid women during pregnancy, neither in women with sporadic or recurrent miscarriages or to decrease the rate of preterm delivery. The current 2017 ATA guidelines also confirm that there is still insufficient evidence to determine whether LT4 treatment decreases pregnancy loss risk in these women. However, they add that administration of LT4 to TPOAb-positive, euthyroid pregnant women with a history of prior miscarriage may be reasonably considered, especially when no other cause for prior pregnancy loss has been identified. In agreement with the previous guidelines, the 2017 guidelines maintain that there is no sufficient evidence to recommend for or against treating these women to prevent premature delivery.

HYPOTHYROIDISM AND PREGNANCY

Hypothyroidism is the most common form of thyroid dysfunction during pregnancy. It can be defined as overt hypothyroidism, when there is a raised TSH and low serum FT4 outside the trimester-specific reference ranges, or as subclinical hypothyroidism, when there is an elevated maternal TSH but normal FT4 concentrations. There is yet another entity referred to as isolated hypothyroxinemia defined as low maternal FT4 in the absence of TSH elevation. However, this definition lacks consensus as, in most studies, it is defined as an FT4 below the 2.5th or the 10th percentile but, in the recent ATA guidelines, it is defined as a FT4 concentration in the lower 2.5th – 5th percentile. The prevalence of subclinical hypothyroidism, that can go from 3.5% to 18% of all pregnancies, depending on the used upper limit of TSH (4), is

much higher than that of overt hypothyroidism that accounts only for <1% of gestational hypothyroidism (2, 4). Isolated maternal hypothyroxinemia is also prevalent, affecting 1% - 2% of pregnant women in iodine-sufficient regions (54). The 2017 ATA guidelines recommend that maternal hypothyroidism should be defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range, making the serum TSH the main determinant of maternal thyroid status. As discussed above, this limit has substantial population variances that can be partly explained by differences in their iodine status and other factors such as ethnicity, BMI and thyroid autoimmunity (14, 15, 19). For these reasons, in their 2011 guidelines, the ATA defended fixed upper limits for serum TSH concentration that were 2.5 mU/l in the first trimester and 3.0 mU/l in the second and third trimesters. However, in their newly revised guidelines, they continue to propose that population and trimester-specific reference ranges should be applied but, in case they are not available, an upper reference limit of ≈ 4.0 mU/l may be used, reflecting a current more liberal upper TSH reference range.

In areas of insufficient iodine intake, iodine deficiency remains the primary cause for maternal (and fetal) hypothyroidism. However, not only iodine deficiency can cause hypothyroidism, but iodine excess may also have negative repercussions in thyroid function. Teng *et al.*undertook a five-year follow-up study of three cohorts with different levels of iodine intake as defined by UIC: mildly deficient, more-than-adequate and excessive intake. The prevalence of overt and subclinical hypothyroidism was 3.2 times higher in the more-than-adequate iodine intake region and 6.8 times higher in the excessive iodine intake region. Furthermore, they found that among subjects who had high levels of thyroid auto-antibodies at baseline, the rate of progression to hypothyroidism correlated directly with iodine intake, suggesting that

high iodine intake may exacerbate thyroid autoimmune disease, increasing the risk of hypothyroidism (34, 55). In iodine sufficient regions, the most common cause for hypothyroidism is autoimmune thyroiditis. Indeed, epidemiological studies in the first half of pregnancy have shown that thyroid auto-antibodies were present in 70% - 90% of women with overt hypothyroidism, 30% - 60% of women with subclinical hypothyroidism and about 10% of women with isolated hypothyroxinemia (2). Other causes of hypothyroidism include previous thyroidectomy, radioiodine ablation for treatment of hyperthyroidism, radiotherapy to the head and neck and thyroid dysgenesis (2, 56). The most common cause of isolated maternal hypothyroxinemia is iodine deficiency, mostly mild-to-moderate iodine deficiency, but other newly identified factors have been associated with this entity such as obesity, iron deficiency, placental angiogenic factors and environmental disruptors like thiocyanate, present in cigarette smoke, that is a competitive sodium iodine symporter inhibitor (54). Overall, women with isolated hypothyroxinemia had worse metabolic parameters with increased obesity, glycaemia, insulin resistance and less favorable lipid profile compared to euthyroid women (57). Finally, iron deficiency can impair thyroid hormone synthesis and metabolism by reducing the activity of the heme-dependent thyroid peroxidase (58).

As illustrated in Table 1, overt maternal hypothyroidism is associated with an increased risk of adverse obstetric outcomes including pregnancy loss, pre-eclampsia, gestational hypertension, premature delivery, low birth weight, placental abruption, postpartum hemorrhage, neonatal respiratory distress and with negative effects on neurocognitive function of the child (2, 39, 56). The most severe effect of maternal hypothyroidism on fetal brain development is endemic cretinism. Still, other neurodevelopmental disorders can occur in the absence of an adequate supply of thyroid hormones to the fetus, varying from specific disabilities to global impairments. A recent

review described a hypothesis of fetal programming by maternal thyroid dysfunction, linking an abnormal maternal thyroid function in pregnancy to a higher susceptibility for the later onset of neurodevelopmental disorders via subtle changes on early brain development (59). This linkage was exemplified by seizure disorders whose structural abnormalities include malformations of the cortex and the hippocampus. In the studied animals, offspring exposed to maternal hypothyroidism had structural alterations of the neocortex with abnormal migration and cytoarchitecture in the somato-sensory cortex and hippocampus. It was also observed that these rats were more likely to present with seizures to an acoustic stimulus compared to normal rats. The same authors studied the association of maternal thyroid dysfunction with the risk of developing seizure (neonatal seizure, febrile seizure or epilepsy) in nearly 1.7 million children born in Denmark who were followed to the age of 30 years (60). They found that children born to mothers who were only diagnosed with hypothyroidism in the years after the pregnancy had an increased risk of all types of seizures under study, leading the authors to speculate whether these women had already some degree of thyroid hypofunction during pregnancy which was, at the time, undiagnosed and untreated.

In comparison with overt hypothyroidism, in which there is unequivocal evidence for adverse events, the effects of subclinical hypothyroidism on pregnancy are still unclear, being associated with an increased risk of adverse pregnancy outcomes (Table 1) in most but not all studies (44, 61-65). This can be partly explained by the fact that many studies regarding this subject define subclinical hypothyroidism differently, using different cut-offs for an elevated TSH concentration. Furthermore, many studies do not take into consideration thyroid auto-antibodies status which is a major risk factor for subclinical hypothyroidism (36). In fact, the combination of subclinical hypothyroidism and thyroid autoimmunity is associated with a higher risk of pregnancy

complications (44, 47). In contrast to its association with adverse pregnancy outcomes, the negative effects of subclinical hypothyroidism on fetal neurocognitive development are less clear. A study embedded in the Generation R Study in the Netherlands evaluated maternal thyroid function in early pregnancy and cognitive function in early childhood and concluded that maternal TSH was not related to the cognitive outcomes. It was stated that, most likely, maternal TSH values higher than the reference-range would not lead to neurodevelopment deficits of the offspring if not accompanied by low FT4 levels (66). Similarly, in a population-based cohort in Spain, the authors studied the effects of subclinical hypothyroidism during pregnancy on neurodevelopment of the child and found no association between TSH levels and mental or psychomotor scores (67). In summary, even though an association between subclinical hypothyroidism and poorer neurocognitive development is biologically plausible, it has not yet been clearly demonstrated.

Overt hypothyroidism	**Subclinical hypothyroidism**
Adverse pregnancy outcomes	Adverse pregnancy outcomes
Pregnancy loss	Pregnancy loss
Gestational hypertension	Gestational diabetes
Pre-eclampsia	Pre-eclampsia
Placental abruption	Growth restriction
Preterm delivery	Preterm delivery
Low birth weight	Neonatal death
Postpartum hemorrhage	Neurodevelopmental disorders
Neonatal respiratory distress	(plausible but lacks clear demonstration)
Neurodevelopmental disorders	
Endemic cretinism	
Impaired mental function	

Table 1: Adverse pregnancy and fetal outcomes associated with overt hypothyroidism and subclinical hypothyroidism

While subclinical hypothyroidism is associated with adverse pregnancy outcomes, hypothyroxinemia is mostly associated with adverse neurocognitive outcomes in the child. In 3659 mother-child pairs from a population-based cohort in Rotterdam, both mild and severe maternal hypothyroxinemia, defined as FT4 concentrations below the 10^{th} and 5^{th} percentiles, respectively, were associated with a higher risk of expressive language delay at 18 and 30 months. Severe maternal hypothyroxinemia also predicted a two-fold higher risk of nonverbal cognitive delay at 30 months (66). Ghassabian *et al.* have been able to study cognitive performance later on in life by follow-up of their participants over the years. They investigated the effects of maternal hypothyroxinemia in early pregnancy, defined as a FT4 < 5^{th} percentile, on child IQ levels at 6 years of age (68). Children of hypothyroxinemic mothers scored 4.3 points lower than children of euthyroxinemic mothers. Trying to establish a neurobiological link between maternal hypothyroxinemia and adverse consequences on child neurodevelopment, they also investigated brain morphology at 8 years of age using magnetic resonance imaging in a subset of 652 children (27 cases and 625 controls). However, no differences in brain morphology were found. The authors propose several explanations for this finding, one of them being that structural alterations resulting from hypothyroxinemia may not be global but, instead, involve sub-regions of the brain. Children exposed to hypothyroxinemia also have more ADHD (30) and greater autistic-like behavior (70). Overall, available studies appear to show an association between hypothyroxinemia and subnormal neurocognitive development of the offspring with lower IQ, language delay, worsened motor function and an increased

risk for neuropsychiatric disease. Currently, hypothyroxinemia is not associated with a consistent pattern of adverse pregnancy outcomes (71).

As mentioned above, numerous studies confirm the detrimental effects of overt hypothyroidism on pregnancy outcomes and on neurodevelopment of the child. Therefore, as shown in Figure 1, it is consensual that treatment of overt hypothyroidism is recommended in pregnancy, with a target TSH in the lower half of the trimester-specific reference range. On the other hand, for subclinical hypothyroidism, the recommendations have experienced some modifications over the years, trying to encompass the best available evidence. Some studies suggest that LT4 treatment reduced mostly the risk of miscarriage and preterm delivery (53, 72). The new ATA guidelines recommend, at first, evaluation for TPOAb status in pregnant women with TSH concentrations > 2.5 mU/L, given that obstetrical outcomes are poorer in women with subclinical hypothyroidism who are thyroid-antibody positive. LT4 therapy is recommended for TPOAb-positive women with a TSH greater than the pregnancy-specific reference range and it may be considered with TSH concentrations > 2.5 mU/L and below the upper limit of the pregnancy-specific reference range. Whereas the 2011 guidelines referred that there was insufficient evidence to recommend for or against universal LT4 therapy in TPOAb-negative women with subclinical hypothyroidism, the recent guidelines recommend treatment for TPOAb-negative women with a TSH > 10 mU/L and claim that it may be considered for TPOAb-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10 mU/L. At present, there are no data that demonstrates beneficial effects of LT4 therapy on isolated hypothyroxinemia. Two randomized prospective intervention trials were conducted to date and both failed to show beneficial effects of LT4 therapy on cognitive development (73, 74). In the Controlled Antenatal Thyroid Screening Study (CATS),

women in the screening group with TSH > P97.5, FT4 < P2.5 or both were treated with a starting dose of 150 µg LT4 with subsequent dose adjustments according to thyroid function testing. An intention-to-treat analysis showed no difference in the children's IQ at 3 years of age between the treated and the non-treated group. The second study screened women for subclinical hypothyroidism and hypothyroxinemia and, in separate trials for the two conditions, they were randomly assigned to receive LT4 or placebo. The results showed no significant difference in the offspring IQ at 5 years of age between the treated and untreated groups. It should be noted that, in both studies, treatment was only started at a mean gestational age of 13 and 17 weeks, respectively, which constitutes a potential limitation, since brain development is mainly dependent on maternal thyroid hormones in the first trimester of pregnancy, making timing of LT4 replacement a critical aspect. For now, until further trials on treatment of hypothyroxinemia early in pregnancy are available, isolated hypothyroxinemia should not be routinely treated.

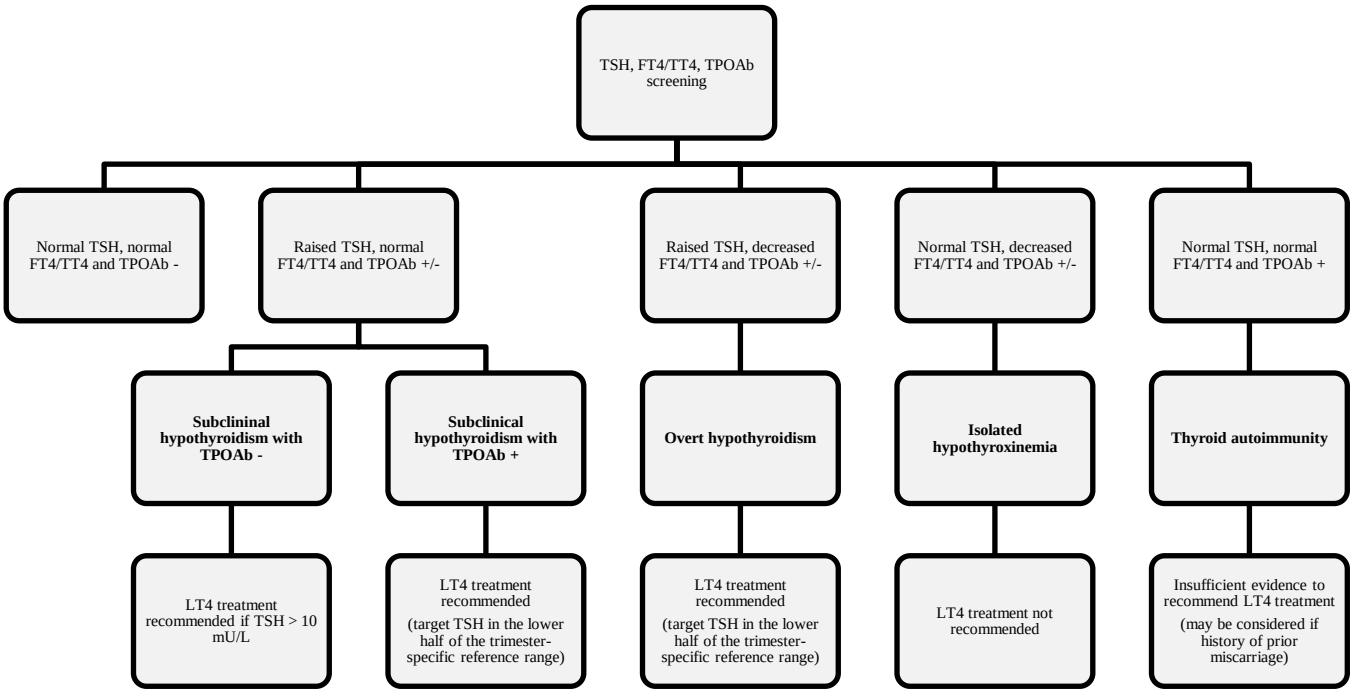

Figure 1: Algorithm for screening and management of hypothyroidism during pregnancy based on recommendations of the 2017 ATA guidelines. Adapted from "Hypothyroidism in Pregnancy" by Teng W, Shan Z, Patil-Sisodia K, Cooper DS, 2013, *The Lancet Diabetes and Endocrinology, Volume 1,* 228-37

In women with a previous diagnosis of hypothyroidism, the increased requirement for thyroxine, or exogenous LT4, increases as early as the fifth week of gestation and stabilizes around week 20, maintaining a plateau until delivery (2). This information provides the basis for recommending adjustments of LT4 dosage and the timing of follow-up intervals for TSH in treated patients. An increase in LT4 dose should be made as soon as possible after pregnancy is confirmed, as maternal hypothyroidism tends to worsen due to the increased demand for thyroid hormones. Overall, 50% – 85% of treated hypothyroid women will have to increase their dose of LT4 during pregnancy (75, 76). In what concerns surveillance of women with hypothyroidism, or at risk for hypothyroidism (thyroid-antibody positive women, post-hemithyroidectomy or treated with radioactive iodine), these patients should be more closely monitored with a serum TSH measurement every 4 weeks until mid-gestation and, at least, once near 30 weeks gestation. It is recommended a monthly thyroid function testing in the first 20 weeks of pregnancy because this strategy could detect 92% of abnormal TSH values in comparison to 73% in a 6-weekly thyroid function assessment (77). Finally, after delivery, maternal requirement for thyroid hormones should return to a pre-pregnancy dose or it may even be stopped in women who started LT4 during pregnancy (56). It is also recommended a follow-up thyroid function testing at approximately 6 weeks postpartum. This assessment is important because, in women started on LT4 during pregnancy for thyroid autoimmunity that now present with normal TSH values, treatment may be interrupted. A small minority of thyroid-antibody

positive women with subclinical thyroid dysfunction in pregnancy may require lifelong replacement treatment. This was demonstrated by a follow-up study of women with subclinical hypothyroidism in pregnancy, that reported that the majority (75%) of women had normal TSH values after pregnancy but 20% remained subclinically hypothyroid and 5% were on LT4 treatment when reassessed 5 years postpartum (78). Both TPOAb-positivity and TSH concentrations > 5 mU/L in pregnancy were predictive of later persistent hypothyroidism.

SCREENING FOR THYROID DYSFUNCTION

Universal screening for thyroid dysfunction remains one of the biggest controversies of management of thyroid disease during pregnancy. To be accepted, universal screening requires fulfillment of some key criteria: 1) the disease is common; 2) a screening tool is available, reliable and inexpensive; 3) an accepted treatment exists that favorably influences the disease; 4) the intervention is cost-effective and 5) there is an agreed policy on whom to treat (79). According to these criteria, sufficient evidence exists to support universal screening of overt thyroid dysfunction during pregnancy. As previously discussed, thyroid disease in pregnancy is common, both testing and treatment are available and improve maternal/fetal outcomes and the cost-effectiveness of universal screening is favorable in comparison with studying targeted groups of pregnant women (80). Meeting most of the criteria, one is lacking, as a policy on whom to treat is yet to be agreed upon. While treatment of overt hypothyroidism is universally recommended, there is great discussion as to whether subclinical hypothyroidism and isolated maternal hypothyroxinemia should be treated. Data on treatment effectiveness of subclinical hypothyroidism has yielded mixed results, depending on the considered adverse endpoints (pregnancy complications and neurocognitive outcomes in the offspring). Indeed, some studies suggest benefits of LT4 treatment in this population

(53, 72), while others report no significant difference between treatment with LT4 and no treatment (73). Another argument in favor of universal screening is that it has been shown to be more effective in detecting cases of thyroid dysfunction compared to a case finding approach (81). Vaidya *et al.* examined the efficacy of a targeted high-risk case finding approach in identifying women with thyroid dysfunction during early pregnancy and concluded that testing only these women would miss about one third of women with hypothyroidism. One large randomized study, aiming to compare universal screening vs. case finding in detecting thyroid dysfunction, found that universal screening did not result in a decrease in adverse outcomes compared to the case finding approach. However, the proportion of hypothyroid women with, at least, one adverse obstetrical or neonatal outcome was significantly higher in the low-risk case finding group (because there was no diagnosis and thus they were untreated, 91%) than in the low-risk universal screening group (diagnosed and thus treated, 34%) (82). In the conclusion section, the authors state that their study confirmed that case finding failed to detect most pregnant women with thyroid dysfunction.

On the other hand, certain practicalities make an adequate assessment of thyroid function difficult and cannot be underestimated when proposing universal screening. The use of population, trimester-specific reference ranges is strongly recommended, but they may not be widely available. Furthermore, the establishment of these reference ranges should be done using women without thyroid disease and with optimal iodine intake, which can be challenging in Europe, as many European countries are still mildly iodine deficient (32). This way, the application of American guidelines in Europe should be done carefully. There is also uncertainty regarding the most appropriate initial screening test because the most effective screening strategy may require multi-modal testing, with measurement of FT4 levels and thyroid-antibodies testing, instead of only

using TSH evaluation, as it is recommended in consensus guidelines. Moreover, in order to magnify the benefits of LT4 treatment, screening for thyroid dysfunction should happen early in pregnancy, which implies the need for obstetricians and other physicians most likely to encounter pregnant women in daily practice, to have the capacity to identify and manage thyroid dysfunction in early pregnancy (83). At last, as previously mentioned, the effectiveness of LT4 treatment in subclinical thyroid dysfunction has not yet been clearly demonstrated. Therefore, all the above uncertainties prevent the recommendation for or against a universal screening strategy.

Currently, guidelines recommend identification of pregnant women at high risk for thyroid dysfunction and their subsequent evaluation by serum TSH with reflex thyroid-antibodies if TSH is 2.5 – 10 mU/L. For that purpose, the following risk factors for thyroid disease should be evaluated (Box 1): history of thyroid dysfunction (hypothyroidism/hyperthyroidism); current symptoms or signs of thyroid disease; previously known thyroid-antibody positivity or presence of a goiter; history of head or neck radiation and prior thyroid surgery; age > 30 years (17); history of type 1 diabetes mellitus (84) or other autoimmune diseases (85); history of pregnancy loss, preterm delivery or infertility (41); two or more prior pregnancies (17); family history of autoimmune thyroid disease or thyroid dysfunction (86); morbid obesity (15); use of amiodarone, lithium or recent administration of iodinated radiologic contrast (87) and inhabiting an area of moderate to severe iodine deficiency (23).

Serum TSH values should be obtained early in pregnancy if the following risk factors for thyroid dysfunction are identified

- History of thyroid dysfunction or prior thyroid surgery
- Current symptoms/signs of thyroid dysfunction or presence of goiter
- Thyroid antibody positivity
- Prior head or neck irradiation
- Age > 30 years
- Type 1 Diabetes Mellitus/other autoimmune diseases
- Family history of thyroid disease
- History of miscarriage or preterm delivery
- Infertility
- ≥ 2 prior pregnancies
- Morbid obesity (BMI ≥ 40 kg/m²)
- Use of amiodarone or lithium or recent administration of iodinated radiologic contrast

Box 1: 2017 ATA guidelines screening recommendations for hypothyroidism during pregnancy

CONCLUSION

Over the past several years, knowledge has been accumulating on the impact of thyroid dysfunction in pregnancy, both in the mother and the fetus, as well as in the postpartum period. First, it is important to be clear on the definitions of normal and abnormal thyroid function during pregnancy which, ideally, should be assessed using population-based reference ranges. Several studies have shown that TSH reference ranges in pregnancy vary between different racial and ethnic groups (14) and that

applying fixed cut-off values for normal thyroid function in pregnancy can be misleading and lead to overdiagnosis of gestational thyroid disease (11). Even though the use of population and trimester-specific reference ranges is preferable, if not available, fixed cut-off values may be used. In fact, one of the most relevant changes from the 2011 to the 2017 ATA guidelines is the establishment of a TSH upper reference limit of 4.0 mU/L, instead of the previous 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimesters (12, 13).

Regarding iodine status, iodine nutrition throughout the world has improved significantly over the past several years. Thus, severe iodine deficiency in its most severe manifestation, that is cretinism, is not common, at least in the developed world. In fact, the subtler degrees of brain damage and reduced cognitive capacity that have been associated with milder iodine deficiency are of much greater public health importance nowadays. Mild-to-moderate iodine deficiency has been associated with impaired cognitive outcomes, as well as ADHD (28, 30). The detrimental effects of severe iodine deficiency and the advantages of its correction are well established (25-27). However, the benefits of correcting mild-to-moderate iodine deficiency are still uncertain, despite some studies suggesting improved maternal outcomes and cognitive function of the offspring with iodine supplementation (29). Pregnant women should ingest and supplement their diet with a daily adequate amount of iodine.

An overview of recommendations of both 2011 and 2017 ATA guidelines shows they have much in common and, yet, both lack strong, conclusive evidence regarding some topics of screening and management of thyroid disease during pregnancy. Namely, management of pregnant women with mild thyroid dysfunction and thyroid auto-antibodies is not consensual. Thyroid auto-antibodies are common in women of childbearing age and have been associated with spontaneous pregnancy loss and

preterm delivery (19, 35). However, controversy remains on treating euthyroid, thyroid-antibody positive women, even though some studies suggest a beneficial effect of LT4 in these women (38). High-quality data from two on-going studies, the TABLET trial and the T4Life trial (43, 52), is needed to undoubtedly conclude about the effectiveness of LT4 treatment in these women. For now, the guidelines state that there is not sufficient evidence to recommend for or against treating these women. Nonetheless, the 2017 ATA guidelines add that administration of LT4 to euthyroid, thyroid-antibody positive women may be reasonably considered in case of recurrent pregnancy loss.

Overt maternal hypothyroidism has been repeatedly associated with maternal and fetal adverse outcomes (2, 56), so it is consensual that overt hypothyroidism during pregnancy should be treated. These women require a more careful monitoring with a monthly TSH measurement until mid-gestation and, at least, once around 30 weeks gestation. The question remains whether treatment of subclinical hypothyroidism could result in fewer maternal and fetal complications. Some studies indicate an increased risk of adverse pregnancy outcomes, mainly pregnancy loss and preterm delivery (44, 61), which is exacerbated by the presence of thyroid auto-antibodies (44). The detrimental neurocognitive effects of maternal subclinical hypothyroidism are less clear and two randomized intervention trials did not show any beneficial effect of LT4 treatment on cognitive development of the child (73, 74). However, both studies recognize that the initiation of LT4 therapy only after the first trimester of pregnancy may have influenced the results. Currently, the ATA guidelines recommend treating women with subclinical hypothyroidism who are thyroid-antibody positive and women with a TSH above 10 mU/L. Isolated maternal hypothyroxinemia has mostly been associated with adverse neurocognitive outcomes such as lower IQ, language delay, poorer psychomotor function (66, 68, 69) and, also, a higher risk of neurobehavioral disorders like autism

(70). The two intervention studies mentioned above (73, 74) failed to find beneficial effects of LT4 therapy on cognitive development of children born to hypothyroxinemic mothers. This way, the guidelines do not recommend its treatment in pregnancy.

Screening for thyroid dysfunction in pregnancy is another controversial matter. Both guidelines recommend screening for high risk patients with known risk factors for thyroid disease such as prior history of thyroid dysfunction, thyroid-antibody positivity, history of autoimmune diseases or family history of thyroid dysfunction, instead of universal screening. However, the justification behind this recommendation is somewhat weak because thyroid disease is common, thyroid function can be adequately assessed with currently available tests, which are inexpensive and widely available, thyroid dysfunction is associated with adverse pregnancy and fetal outcomes that can be mitigated with LT4 therapy and studies have shown that a universal screening strategy is cost-effective (79, 80). However, the complexity surrounding this subject is based on treatment effectiveness, especially in pregnant women with subclinical hypothyroidism. Therefore, a trial screening women preconception and starting early LT4 administration in those with subclinical hypothyroidism (and isolated hypothyroxinemia) is mandatory, in order to clarify the on-going debate on treatment of subclinical thyroid dysfunction and the most adequate screening strategy for pregnant women.

Finally, from the 2011 to the 2017 ATA guidelines, many recommendations have endured six years of clinical and scientific advances and remain practically unchanged, while some relevant improvements have been made, namely in the normal reference range for serum TSH concentrations during pregnancy and management of subclinical thyroid dysfunction. As usual, new knowledge generates new questions and high-quality trial data is still lacking in order to clarify the controversial issues on screening and management of thyroid disorders during pregnancy.

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