CONTROVERSIES IN ENDOCRINOLOGY

On the need for universal thyroid screening in pregnant women

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Abstract

There is a well-known controversy among scientific societies regarding the recommendation to screen for thyroid dysfunction (TD) during pregnancy. Although several studies have shown an association between maternal subclinical hypothyroidism and/or hypothyroxinemia with obstetric problems and/or neurocognitive impairment in the offspring, there is only limited evidence on the possible positive effects of thyroxine (T₄) treatment in such cases. Despite the scarcity of this evidence, there is a widespread agreement among clinicians on the need for treatment of clinical hypothyroidism during pregnancy and the risks that could arise due to therapeutic abstention. As maternal TD is a quite prevalent condition, easily diagnosed and for which an effective and safe treatment is available, some scientific societies have proposed to assess thyroid function during the first trimester of pregnancy and ideally before week 10 of gestational age. Given the physiologic changes of thyroid function during pregnancy, hormone assessment should be performed using trimester-specific reference values ideally based on locally generated data as geographic variations have been detected. Screening of TD should be based on an initial determination of TSH performed early during the first trimester and only if abnormal should it be followed by either a free or total T₄ measurement. Furthermore, adequate iodine supplementation during pregnancy is critical and if feasible it should be initiated before the woman attempts to conceive.

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Introduction

Over the last 20 years, the association between thyroid function alterations and/or thyroid autoimmunity and its adverse effects on pregnancy, the mother and the unborn child has become more than evident. During this time period, a general appreciation has been developed among clinicians regarding the important adaptive changes that occur in maternal thyroid economy during pregnancy (1). Furthermore, research has more firmly established the impact of iodine deficiency, even mild to moderate, on the mother, pregnancy outcome, and developing fetus (2). In parallel to this, progress in laboratory medicine has provided more precise methods of hormone testing, which in combination with epidemiological studies have resulted in the establishment of normative values for thyroid function tests in each of the three trimesters of pregnancy. Recent research has also provided a better understanding of the fetal consequences of varying degrees of severity of maternal hypothyroidism and the related timeframe throughout gestation for achieving healthy pregnancy outcomes and a normal neuropsychological development of the progeny (3). In this regard, data obtained from clinical studies indicating the necessity of increasing the dose of levothyroxine (LT₄) in most women with pregestational hypothyroidism in order to maintain euthyroidism throughout pregnancy are critical (4, 5). The negative influence of thyroid autoimmunity (TAI), even without hormonal thyroid dysfunction (TD), on miscarriage and preterm delivery has been well established in the last decade (6, 7, 8) and adds more arguments to take action so as to prevent these thyroid-related threats to pregnant women and newborns.

These aforementioned advances in the understanding of the physiology and pathophysiology of the thyroid gland and the adverse impact of thyroid abnormalities during pregnancy have led to a vigorous scientific debate on the advisability of universal thyroid screening, either when preparing to conceive or at an early stage of pregnancy. Other factors that impact the debate on whether to perform universal screening for thyroid disease during pregnancy include the following: i) most common thyroid disorders that may impact pregnancy outcome and fetal health, namely TD and TAI, generally do not cause symptoms or signs and therefore the diagnosis is virtually exclusively biochemical ii) Subclinical hypothyroidism (SCHypo), excluding euthyroid women who are thyroid antibody positive (Abs), is the most common thyroid disorder during pregnancy. Any consideration related to screening of thyroid function in these women

will depend on the clinical impact of SCHypo on the fetus and the potential benefits of its treatment. iii) The maternal thyroid economy undergoes significant physiological changes of adaptive nature, with varying concentrations of peripheral thyroid hormones and thyrotropin (TSH) throughout pregnancy, thus requiring a consistent normative data according to the gestational age for a correct interpretation, especially in the range of subclinical thyroid disease.

The alternative approach to universal screening is to screen women at increased risk for thyroid disease. In this paper, we present and discuss the current recommendations of different scientific societies, as well as individual expert opinions, on universal vs selective screening.

To screen or not to screen: a continuous discussion between experts

In women with clinical hypothyroidism (Chypo) diagnosed before pregnancy, a systematic evaluation of thyroid function tests before conception or at first antenatal visit should be performed by the general practitioner or the endocrinologist for adjusting substitution treatment (5, 9). To date, the discrepancies in relation to the recommendation of universal screening of TD in pregnancy are evident, and detractors base their position on data demonstrating the inconsistency of the benefits of LT₄ treatment in women with SCHypo (10, 11). The American College of Obstetricians and Gynecologists (12), the American Thyroid Association (ATA) (13), and the American Association of Clinical Endocrinologists (AACE) (14) are proponents of selective but not universal screening. Indicative of the controversy surrounding universal screening is the lack of unanimity within the 2012 Endocrine Society guidelines, resulting in a majority opinion advocating selective screening and a minority opinion recommending universal screening (15). It should be noted that other scientific societies are beginning to recommend universal screening, such as the Spanish Society of Endocrinology and Nutrition (SEEN) (16, 17, 18). Similarly, Stagnaro-Green (19) argued that universal screening is warranted based on the deleterious impact of undiagnosed and therefore untreated overt hypothyroidism on the mother and fetus, and neurocognitive development of the unborn child.

Screening only women at high risk of TD raises multiple questions including how is high risk defined, and how will these women be identified, monitored, and

treated. Obviously, all this work should preferably be done before conception or as early as possible during pregnancy (13, 20). Poppe *et al.* (6) supported a selective screening of high-risk women, emphasizing the efficiency of this approach with a special attention to infertile women. However, focusing exclusively on high-risk pregnancies could leave between one- and two-thirds of women with SCHypo undiagnosed (21). A recent questionnaire concerning the clinical practice of screening for thyroid disease in pregnancy included 605 members of the European Thyroid Association (22). Forty-two percent of responders screen all women for TD, 43% perform targeted screening of the high-risk group, whilst 17% do not perform screening. These results highlight the difference of opinion among the European endocrinologists. Based on the 2011 thyroid and pregnancy guidelines, the ATA (13) recommends a selective screening for thyroid disease in women, which is represented in Table 1.

Although all these conditions seem very reasonable, when their frequency are reviewed in European countries such as Spain, it is remarkable how many women are at risk. Furthermore, it is noteworthy that the population that would be classified as free of risk is decreasing over the last decades. For example, in regards to obesity, the scenario is currently dramatic in some countries due to the extraordinary increase in the prevalence of obesity in youngsters. In this regard, the prevalence of obesity in the Spanish childhood population is currently around 13% (23), increasing steadily thereafter and also increasing in pregnant women. Moreover, due to the economic crisis and the long and competitive professional careers it is more and more common for the first and subsequent pregnancies to take place after the age of 30. The cut-off

age of 30 as a risk factor for high risk screening is included in both the ATA 2011 and the Endocrine Society 2012 guidelines on thyroid and pregnancy (13, 15), although this issue has been highly debated in the last years (24, 25). However, even if some studies have demonstrated an increasing rate of hypothyroidism with increasing age (26, 27), its prevalence at age <30 should not be disregarded and such potential cases, although lesser, deserve also to be detected. Moreover, as the arithmetic sum of all the proposed risk factors in the entire European population of women of childbearing age may lead us to the conclusion that more women would be classified as at risk than would be considered risk free, this would support universal screening.

What does screening imply?

Screening is the systematic and active search of a health problem by applying a test on a large scale in apparently healthy people. The basic idea is that early detection and treatment are beneficial at individual and community level. Screening tests are not usually intended to be diagnostic; therefore, positive results need to be confirmed later on. In 1968, the World Health Organization (WHO) published the principles that should govern, and the tools that should be used in, a screening program (28, 29). The WHO criteria are currently upheld from the perspective of public health policies, and have been adapted and updated to help decision-making (30). Screening criteria can be grouped into three categories: i) the disease or health problem should be serious, highly prevalent, and have a detectable preclinical stage (a good understanding of the natural history of the disease with a detectable preclinical stage is required); ii) the screening test should be sensitive and specific; simple and inexpensive; safe, acceptable, and reliable; easy to perform; and ideally cause virtually no discomfort; and finally iii) the diagnosis of the health problem requires adequate facilities with the equity of access and availability to effective, acceptable, and harmless treatment.

Screening should not be instituted if early treatment is ineffective and does not modify the natural history of the disease. Lastly, screening should be cost-effective in order to be successful; according to this principle, it is noteworthy that an early detection of the disease should represent a substantial improvement in the health of the population and the action would have a favorable cost:benefit ratio.

Table 1 High-risk conditions for thyroid diseases in pregnant women.

History of previous thyroid dysfunction, goiter, positive thyroid antibodies, cervical irradiation, or thyroid surgery
Age >30 years
Family history of thyroid disease
Presence of clinical signs or symptoms of hypothyroidism (although only 30% of cases usually show clinical symptoms)
Diagnosis of type 1 diabetes mellitus or any other autoimmune disease
History of repeated abortions, prematurity, or infertility
Morbid obesity
Treatment with lithium, amiodarone, or recent administration of iodinated contrast
Living in an area with moderate to severe deficiency of iodine

Why should we perform universal screening of TD in pregnant women?

It is not easy to establish consensus when the condition to be screened is not a single disease but diverse disorders grouped under the concept of 'thyroid dysfunction', during a specific period of time and affecting a physiologic and dynamic process, such as pregnancy. Furthermore, the potential impact of TD may be heterogeneous, depending on its cause and/or severity. As stated by Alexander (31), TD in pregnancy meets several characteristics supporting its active screening, as it is frequent in women of childbearing age, detection is easy with a simple measurement of TSH and may be treated properly and safely with a cheap compound, which is T₄. Following the criteria established by Beaglehole (32), the statement by Alexander could be assessed by answering the following questions: Is TD during pregnancy really a health problem? Do we have available simple and reliable diagnostic tests? Is universal screening cost-effective? Is there a simple, safe, and economically affordable treatment? And how and when should all of this occur?

Is TD during pregnancy really a health problem?

TD prevalence during pregnancy as a health problem ► Data on the prevalence of hypothyroidism in pregnant women in European countries are limited (21, 33, 34, 35, 36, 37, 38) and the reported figures range between 4.6–11.8% for SCHypo and 1.6–2% for Chypo (35). In the USA, Stagnaro-Green *et al.* (39) reported a lower prevalence of Chypo of about 0.5% in women of childbearing age. Two recent reports have indicated a prevalence of 2.5% of Chypo in a large population of pregnant women in the USA (40) and a 12.5% prevalence of high TSH values in a region of Italy (41). Maternal hypothyroxinemia, defined as a decreased serum concentration of free T₄ (FT₄) with a normal TSH, is about 150 times more frequent than congenital hypothyroidism (3); it reflects an underactive thyroid gland, whose more frequent cause is the nutritional deficiency of iodine (42). On the other hand, between 5 and 14% of healthy pregnant women show detectable anti-peroxidase and/or anti-thyroglobulin Abs (6, 43), which are associated with higher concentrations of TSH and lower FT₄ than pregnant women with negative thyroid autoimmunity (44). Regarding hyperthyroidism, prevalences of Grave's disease, with ranges between 0.1 and 1% (45), and transient gestational hyperthyroidism syndrome, with ranges between 1 and 3%, have been reported (46).

Table 2 Alterations associated with thyroid dysfunction in women and during pregnancy.

Obstetric complications associated with maternal hypothyroidism
Fertility problems
Endometriosis ^a
Ovarian failure ^a
Miscarriage ^{a,b}
Fetal death
Prematurity ^{a,b}
Intrauterine growth retardation ^a
Hypertensive disease
Pre-eclampsia ^{a,b}
Placental abruption ^a
Fetal hyperthyroidism ^a
Impact of maternal thyroid dysfunction in the offspring
Perinatal mortality ^{a,b}
Decreased neuropsychological development
Sepsis ^a
Respiratory distress syndrome ^a
Cardiomyopathy ^a
Low birthweight ^a
Large-for-gestational-age infants
Neonatal hyperthyroidism ^a

^aAlso associated with thyroid autoimmunity.

^bAssociated with maternal hyperthyroidism.

Obstetric complications associated with TD ► There is a known association between hypothyroidism and fertility problems (Table 2), although recent studies have shown that hypothyroidism does not preclude the possibility of conceiving (6, 47). A high percentage of women with Chypo or SCHypo become pregnant without being treated with T₄ (48). Abortion and stillbirth have been highly associated with TD, as well as endometriosis and ovarian failure, mostly in women with TAI (6). The success of assisted reproduction is reduced in women with TAI whose TSH is also elevated (49). The risk of intrauterine fetal death is increased in women with >30 weeks of gestational age when TSH is >6 mIU/l (odds ratio 4.4) (50), and in general the risk of abortion clearly increases either in Chypo or SCHypo (51, 52, 53). Intrauterine growth retardation has also shown a positive correlation with the degree of maternal hypothyroidism, either SCHypo or Chypo (54). Hypertensive disease of pregnancy also shows a correlation with concentrations of TSH and endothelin, in parallel with the severity of hypertension (55, 56, 57). Placental abruption has been reported to be three times more frequent in SCHypo (37). Prematurity is also strongly associated with maternal Chypo or SCHypo (58, 59). A recent systematic review has demonstrated an increased risk of complications, especially pre-eclampsia, perinatal mortality, and recurrent miscarriage in pregnant women with SCHypo or with positive thyroid autoantibodies (60).

Impact of maternal TD in the offspring ► In 1999, Haddow *et al.* (9) observed that at 9 years of age, children of women with undiagnosed Chypo (TSH above the 98th percentile) during pregnancy had significantly lower scores in neuropsychologic tests related to intelligence, attention, language, reading ability, school performance, and visual motor performance. Other studies have linked SCHypo, TAI, or hypothyroxinemia in the mothers with poorer results on tests of intelligence and motor skills in their children (61). The effect of maternal hypothyroxinemia has generated a broad debate about its causal involvement in impaired neuropsychological development of the progeny. Although several authors (62, 63, 64, 65, 66) have shown that maternal hypothyroxinemia, defined as $FT_4 < 10$ th percentile with a normal TSH, during the first trimester of gestation is associated with decreased neuropsychological development of the children, a recent study by Craig *et al.* (67) has not confirmed these findings. However, already in 2000, Morreale de Escobar (3) presented epidemiological and experimental evidence strongly suggesting that hypothyroxinemia detected during the first trimester, irrespective of whether TSH was increased or not, was associated with a higher risk of poor neuropsychological development of the progeny, mostly due to a decreased availability of T_4 to the developing fetal brain tissues (68). Later on in 2009, a study by Berbel *et al.* (36), using stringent selection criteria for the assessment of neuropsychological parameters in the studied population, clearly showed the relationship between hypothyroxinemia and impaired functional brain maturation. Mannisto has recently reported that maternal thyroid disorders, either hyperthyroidism or primary hypothyroidism, were associated with multiple adverse outcomes in the offspring, including sepsis, respiratory distress syndrome, transient tachypnea, and apnea (69). Concordant changes in the concentrations of TSH in the children of mothers with TD have also been described, as children of hypothyroid mothers show significantly higher TSH levels than controls and children of hyperthyroid mothers have lower levels of TSH. Whether these hormonal changes confer an increased risk of thyroid disease in the long term in these children is unknown (70).

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

Nowadays, modern societies have experienced a change in the paradigm of medical care, and particularly pregnant women demand a thorough study of all matters relating to

their babies' health during gestation (71). The possibility of detecting pregnant women with TD during their pregnancy and thus the possibility of preventing neurological aftermath in the offspring are no longer a debate limited to scientific societies, but it has begun to generate a social dialogue, as for example reflected in some American newspapers (72). The study of thyroid function in the first trimester of pregnancy requires a single blood determination that could be done in conjunction with the rest of the many analytical explorations performed at the first obstetrical visit. Curiously, most of the routine analyses done at the time of confirmation of pregnancy deal with medical problems of far less prevalence than TD, but which have been established as routine during pregnancy many years ago, some of which are performed simply due to clinical inertia.

TSH is a very sensitive marker of thyroid dysfunction during pregnancy (18, 73). This is true despite the significant effect of β -HCG on TSH concentrations, especially in the first trimester. During the first trimester, β -HCG induces a decrease in circulating TSH, and as a consequence reference values have been modified accordingly. Consequently, utilizing non-gestational normal values during pregnancy may lead to diagnostic errors (74). In contrast, the measurement of maternal FT_4 with the immunoassay techniques currently used presents some difficulties due to insufficient accuracy by virtue of the interference of pregnancy-modified plasma proteins. It has been recently shown that certain FT_4 immunoassays can be quite similar to tandem mass spectrometry, which in turn has proven to have a high correlation with equilibrium dialysis, which is the gold standard for measurement of FT_4 during pregnancy (75, 76). The determination of total T_4 (TT_4) has also been proposed as an alternative method for evaluating thyroid function during pregnancy, as TT_4 measurements are performed by a more robust methodology than those used for FT_4 . The increase in TT_4 due to the increase in placental β -HCG is more predictable and it appears that the reference values established in different populations are more comparable and probably more reliable than those obtained for FT_4 . Moreover, it has been proposed that reference values for TT_4 of pregnant women may be confidently obtained simply by multiplying by 1.5 the reference values of the nonpregnant population (74). However, the potential advantages of the TT_4 have been questioned due to its close relationship with the variability of thyroid-binding globuline (TBG) (77). FT_4 index (FT_4I) is a calculated ratio based on two estimates, namely an estimate of triiodothyronine (T_3) resin uptake and an immunoassay

estimate of TT₄. The T₃ resin uptake test estimates TBG concentrations by adding a known excess amount of ¹²³I-labeled T₃ to a measured volume of serum (78). Currently FT₄I, considered as obsolete, could still be a good method for situations when TBG concentrations are dynamically modified, as occurs during pregnancy (79). However, this option is discussed by Soldin (78) as FT₄I frequently fails to completely correct for the TBG-induced increase in TT₄.

Given the significant changes in the concentrations of thyroid hormones throughout gestation (80), the ATA has recommended that the formulation of the reference values should be performed not only for each trimester of pregnancy but also for each specific geographical region (81) and probably also taking into account the importance of potential variations between the technical methods of measurement. In Spain, for example, different regional studies have been performed (43, 82, 83, 84) aiming to determine the reference range for thyroid hormones in pregnant women. The recent ATA guideline recommends that in the absence of local reference values, the upper normal value for TSH in pregnant women should be 2.5 mUI/ml in the first trimester and 3 mUI/ml in the second and third trimesters. This value of 2.5 mUI/ml was chosen not only because it is near the 97.5 percentile (43, 85, 86) but also because higher values are associated with higher fetal morbidity (5, 87).

Is universal screening cost-effective? Is there a simple, safe, and economically affordable treatment?

The purpose of universal prenatal diagnosis of maternal TD is to intervene therapeutically in crucial stages of fetal development. In this sense, the most ambitious goal of universal screening for TD in the first trimester of pregnancy is to prevent irreversible situations and provide adequate amounts of iodine and T₄ to enable the brain of the fetus to develop in optimal conditions (88, 89, 90). Berbel *et al.* (36) demonstrated that early treatment with potassium iodide in hypothyroxinemic pregnant women resulted in T₄ concentrations that were normalized as well as better scores of psychomotor tests in the progeny of these mothers. Furthermore, according to the results of Negro *et al.* (91), only 40 women would need to be screened to prevent a single adverse event.

This compares extremely favorably in comparison with other health problems in which screening is accepted, such as hypercholesterolemia or hypertension (31). The results of a study of antenatal thyroid screening and childhood cognitive function (92) indicated that T₄

treatment of pregnant women with SCHypo or isolated hypothyroxinemia would bring no benefit to the children of these mothers compared with untreated mothers. Undoubtedly, this study is of great interest. However, study limitations call into question the results of this trial, as Negro has suggested previously (93). The first point is that women started treatment with LT₄ in the second trimester of pregnancy, which is after the critical period of fetal neurodevelopment has been completed. Therefore, what the study demonstrated is that treatment started after week 12 of gestational age does not benefit the neuropsychological development of the fetus, but does not rule out a benefit if treatment was to be initiated early in the first trimester. The second question is that the study did not compare the experimental groups (treated and untreated) with a group of euthyroid mothers. Haddow *et al.* (9) demonstrated significant changes when the experimental design was performed in this way. The absence of this comparison opens the question of whether the delay in diagnosis and treatment may have left children of these hypothyroid mothers with a degree of neuropsychological impairment, as between 12.1 and 14.1% of the studied children had an IQ lower than 85. A third relevant aspect is that no data regarding obstetric problems are reported, probably because they were not included in the outcomes of the study, although it would have been interesting to analyze this issue. In this sense, a reduced incidence of obstetric outcomes in treated women was observed in other studies (91, 94). Thus, the study by Lazarus has not answered the question of whether early diagnosis and treatment (<10 weeks) of hypothyroid women may prevent adverse neuropsychologic effects in the children and the incidence of obstetric complications in the mother.

Three studies have evaluated whether universal screening is cost-effective. Thung *et al.* (89) established a model in which screening is cost-effective, assuming that T₄ treatment of women with SCHypo reduces the incidence of children with IQs <85. This report is limited by the fact that no study to date has demonstrated a positive impact on IQ in the offspring of mothers treated for gestational hypothyroidism. In the second paper by Dosiou *et al.* on this topic, it was determined that first trimester universal screening for thyroid disease was cost-effective when compared with both no screening and selective screening. Universal screening remained cost-effective even when a sensitivity analysis was performed, which assumed no benefit for the treatment of SCHypo (88, 95).

How and when should all this be done?

The question of the temporal therapeutic window ► It is well-known that T_4 requirements in women with previously diagnosed hypothyroidism increase throughout gestation (96). The magnitude of the increase in the dose is variable but ranges between 30 and 50%. To maintain TSH within normal values, the modification of the T_4 dosage is usually performed as soon as pregnancy is confirmed. However, many endocrinologists advise women to increase the T_4 dose once a decision to conceive is made, with the goal of achieving a pre-conception TSH of ~ 1.0 . A delay of 6–10 weeks in the modification of T_4 dosage at the start of pregnancy increases the risk of neurodevelopmental delay of the offspring (36). It is also important to ensure an adequate supply of iodine during pregnancy for many reasons including optimizing the fetal thyroid stores, which are required for its normal start of function at 20 weeks, gestation (13, 97). It has been unequivocally demonstrated that a good nutritional status of iodine, related to iodized salt, bread, and milk consumption over prolonged periods before pregnancy, can reduce the risk of TD during gestation (98, 99). In populations with known iodine deficiency, supplementation with a minimum of 150–200 μg of iodine during pregnancy and lactation ensures the recommended intake is achieved.

Arguments against universal screening

Is TD during pregnancy really a health problem?

TD screening during pregnancy can detect different situations, some of which do not have the absolute certainty of being pathological, and therefore treatment is at least arguable. There is solid evidence that CHypo is associated with multiple adverse outcomes including a negative impact on intellectual and neurocognitive development, as well as gestational hypertension and intrauterine growth retardation (9, 50, 100). However, the relationship between SCHypo and pregnancy-related adverse events is controversial. In fact, even the definition of SCHypo is still debated by some. As a consequence, the impact of its treatment has also been argued. In a prospective study by Casey *et al.* (37), SCHypo was associated with preterm delivery, abruptio placentae, and higher neonatal respiratory distress. However, in a systematic review of maternal thyroid disease and preterm delivery (101), only the work of Casey showed such an association, with two other studies demonstrating low

birth weight. A recent review indicates that pregnant women with SCHypo or thyroid antibodies have an increased risk of complications, especially pre-eclampsia, perinatal mortality, and miscarriage (60). In fact, although there are some data to the contrary, few would argue that a relationship exists between SCHypo, thyroid antibodies, and adverse maternal/fetal impact. The major argument against universal screening and treatment of SCHypo is that there is a paucity of data demonstrating that treatment of SCHypo decreases the risk of these complications. To date, there are only two studies analyzing this point with different results. In the prospective study by Negro *et al.* (91), in which more than 4500 women were randomized to universal or selective screening and treatment was initiated in the first trimester when TSH > 2.5 mUI/ml and anti-TPO Abs were positive, no difference in adverse outcomes was found between the two groups. However, comparison of women identified with TD during pregnancy and treated had statistically fewer adverse outcomes than women with TD who were not identified until after delivery and therefore not treated. On the other hand, the study by Lazarus *et al.* (92) showed no benefit of T_4 treatment of SCHypo pregnant women on their children, although study limitations discussed previously should be taken into account. Thus, it has been argued that until it is irrefutably demonstrated that T_4 treatment may prevent adverse obstetric outcomes, universal screening is not justified (102).

Another important finding of screening, and particularly of universal screening, is isolated maternal hypothyroxinemia. It must be noted that in clinical practice isolated hypothyroxinemia is far from being accepted as an independent thyroid disease and its pathologic significance is under discussion (38, 103). The first question arising when considering this finding is the laboratory method used to develop normative data for this entity. Nevertheless, Pop *et al.* (62, 104) reported that a maternal $FT_4 < 10$ th percentile during the first trimester is associated with a poorer neuropsychological performance of children than higher maternal FT_4 values. The most relevant finding was that in those children whose maternal FT_4 normalized spontaneously in the second or third trimester, or those in whom normal FT_4 was detected during the first trimester but dropped later on, particularly what was not associated with decreased scores on neuropsychological test. These findings emphasize the importance of early screening, as the potential therapeutic window is quite narrow. Craig *et al.* (67) confirmed these findings as no associated neurocognitive deficiencies were found in children of mothers whose

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maternal hypothyroxinemia was detected during the second trimester and onwards. Why TSH does not increase in women with low FT₄ remains to be established (85, 105), although it is known that in areas with low iodine intake, low FT₄ can be found in association with normal TSH (2) due to an increased T₃:T₄ ratio (1). What happens in areas without a clear deficiency of iodine? Interestingly, Mitchell *et al.* (106) found that in pregnant women with a mean concentration of urinary iodine of 134 µg/l, the IQ of the progeny was associated with TSH levels only when multivariate correlations were applied, while FT₄ did correlate but only in univariate models. Moleti *et al.* (107) also observed that 25% of the women in their study had low T₄ values from the early weeks of the second trimester. This decrease could be associated with maternal iodine deficiency and a progressive reduction of intrathyroidal iodine stores. It should be recalled that FT₄ decreases gradually from the beginning of the second trimester (105, 108), thus other factors beside iodine nutrition may participate in the regulation of thyroid function during the second half of pregnancy. Therefore, we have to accept that the implementation of universal screening of thyroid function including FT₄ would identify a certain number of women whose FT₄ would be low and whose supplementation with oral T₄ has yet to be studied. Prospective data generated through universal screening would allow us to recognize the true prevalence and consequences of such a condition.

According to data from NHANES III, in nonpregnant adult populations, FT₄ shows no association with isolated urinary iodine (109). Noteworthy, however, is that data on women of childbearing age and pregnant women show that median urinary iodine has fallen from previous surveys from 320 to 145 mg/l (110). In some prospective studies, no differences in the concentrations of FT₄ were found, regardless of iodine supplementation (111), although in other studies (36, 112) the nonsupplemented control group showed lower FT₄ than the supplemented one. Finally, in another recent study, when pregnant women were universally supplemented with 300 µg of iodine, maternal FT₄ values have shown a lower reduction in the third trimester (68). In this latter study, as well as in others (36), the psychomotor development of these children was improved thus supporting iodine supplementation. Finally, a recent observational study has reported an association of low FT₄ with worse neurocognitive tests in daughters of mothers receiving potassium iodide supplementation during pregnancy (113, 114). Taking all these data together, the more prudent position right now is not to treat isolated hypothyroxinemia due to the lack of evidence (115) of its

effect and the inconsistency of FT₄ measurements, but to ensure sufficient iodine supply during and, even better, before pregnancy. At present, the debate about the relevance of hypothyroxinemia persists and whether to treat or not will require additional studies (66).

Positive thyroid autoimmunity is present in about 10% of pregnant women (116, 117). Three meta-analyses have demonstrated a positive association between thyroid autoimmunity and both abortion and prematurity (8, 116, 118), although this association has not been confirmed in another (101). Negro *et al.* demonstrated that T₄ treatment in women with TAI significantly decreased the number of miscarriages (94, 119). In a Japanese study (120) in which seven different types of autoantibodies were evaluated, excluding anticardiolipin, a similar prevalence of prematurity was observed in the control group compared with women with at least one positive antibody. A review (121) indicates that, besides antiphospholipid antibodies, the presence of other autoantibodies is also associated with recurrent pregnancy loss. The potential causal effect by which thyroid autoimmunity may induce these obstetric problems is not sufficiently known, although it has been suggested that the coexisting anti-TSH receptor antibodies might block β-HCG action (122). Other etiologic possibilities include a subtle degree of hypothyroidism as well as a direct impact of the thyroid antibodies themselves. However, at present it cannot be ruled out that there may be a noncausal association between spontaneous pregnancy loss and thyroid autoantibodies or that the association is simply related to the fact that thyroid antibody-positive women are typically older than women who are thyroid autoantibody negative (118).

As noted earlier, overt hyperthyroidism is associated with abortions, placental abruption, pre-eclampsia, premature delivery, malformations, delayed intrauterine growth, goiter, and fetal and neonatal hyperthyroidism (123). On the other hand, gestational hyperthyroidism, defined as a TSH below the normal first trimester range with a normal FT₄ in a woman who is thyroid autoantibody negative, is not associated with maternal or fetal morbidities (102). In the context of universal screening, gestational hyperthyroidism, which is present in 1.7% (102)–3% (105) of pregnant women, may be associated with hyperemesis gravidarum; treatment with antithyroid medications is not indicated as the vast majority of the times it disappears spontaneously. Furthermore, prospective studies have demonstrated that untreated subclinical hyperthyroidism is not associated with maternal or fetal adverse outcomes. Perhaps this is secondary to the fact that

the fetus is somehow protected from excess FT₄ through the inactivating effect of placental type 3 deiodinase. This is not the case when we are facing the opposite situation of insufficient T₄ supply from the mother to the fetus.

Are simple and reliable diagnostic tests available?

It has been argued that a screening program should not be initiated if the reference range of the biomarkers to be used is not solidly established. In the case of TD in pregnancy, this was true for many years but no longer. Unfortunately, the reference values provided by commercial kits have been established for women who are nonpregnant, but are commonly used in the clinical setting. This is a mistake, as they do not represent the pregnant state or the differences in TSH values in the three trimesters of pregnancy. Reviewing the literature, it is evident that the prevalence of either hypothyroxinemia or a TSH >2.5 µU/ml in pregnant women is quite high. This problem deserves a critical evaluation in order to ensure the validity of such diagnostic cut-off values. The analysis of published data indicates that reference values for TSH in the first trimester are not clearly defined and that different values have been reported (73, 85, 86) in different populations. This disparity is evident even when using the same method of measurement (81). For example, studies that utilized TSH values below the 2.5 percentile have a range from 0.02 to 0.05 mU/ml (86, 124), while the range for the 97.5 percentile varies between 2.15 and 2.3 mU/ml (85, 86, 124, 125). Taking into account the large sample of subjects included in these studies, the data obtained should be rigorously validated before being used in clinical practice. Consequently, if hypothyroxinemia is defined as a value <12 pmol/l for FT₄, a pathological value may be found in as many as 41% of pregnant women. Even using a more conservative FT₄ cut-off of <10.3 pmol/l would result in 10% of women being classified as having an abnormal value. In regards to hypothyroidism, a cut-off value of a TSH >2.5 µU/ml would result in 26.3% of the pregnant population being classified as hypothyroid (126). These figures have raised concern among clinicians and it has been argued that it would result in classifying healthy pregnant women as having a pathological disease.

Although FT₄ measurement during pregnancy has some technical problems and its concentrations are particularly low in the third trimester compared with the nonpregnant population, the combination of a robust screening parameter such as TSH, as the first line approach, complemented with FT₄ measured with a method showing a good correlation with equilibrium dialysis or tandem mass

spectrometry, which could allow a realistic and reliable protocol for detecting TD early in pregnancy. In the near future, tandem mass spectrometry, which has shown a very good correlation with equilibrium dialysis during gestation (76), may be the technique to be used for such purposes. Another factor to consider during pregnancy is the observed inverse relationship between FT₄ and weight (127, 128). In this regard, the recent work of Medici *et al.* (129) has shown a decrease in the weight of children born to mothers with FT₄ in the upper limit of normality. It is difficult to explain the causality of the effect of T₄ level even in the high limit of normality on neonatal weight, thus indicating again the importance of reference values (130).

Treatment of pregnant women with TD is safe and cheap

Although the benefits of Chypo treatment with T₄ are without doubt reported (9, 131), in the case of SChypo, no conclusive work has yet appeared as noted in a recent Cochrane review (132). This review concluded that there is insufficient data supporting the treatment of SChypo, and therefore it is difficult to justify the implementation of a universal screening program to detect TD in the pregnant population. Indeed, another recent review has suggested that the importance of screening is the opportunity of treating overt TD during the first half of pregnancy rather than correcting small modifications of thyroid function tests and that the possible association of small thyroid alterations with pregnancy complications might be attributable to confounding factors more than to a hormonal causal relationship (133). Even accepting this assertion, a screening program would be justified for identifying women with Chypo. On the other hand, it is paradoxical that when treating women with pregestational hypothyroidism, there is a consensus to strive for a pre-conception TSH of 2.5 or lower (13). Thus, why should we also do not do so when a TSH >2.5 is newly detected during or at the beginning of pregnancy as a consequence of a screening program? In this regard, women with known pregestational hypothyroidism are lucky as their fetuses will receive enough T₄, whereas it may not be the case in women with pregestational unknown thyroid function but with a TSH >2.5 during pregnancy. Positive thyroid antibodies information may also be of interest, as their detection is a marker of a pregnancy with a higher risk than average, and therefore a closer follow-up could be performed. The safety of T₄ treatment has also been confirmed in only one study, in which women with positive anti-thyroid antibodies with normal TSH received T₄ (94).

How and when all this should be done? A multidisciplinary effort is necessary

In summary, based on the fact that universal screening is superior in detecting TD cases than selective screening, programs aiming at detection of such disorders are clearly justified in the entire pregnant population. This argument can be supported simply on the importance of detecting and treating overt hypothyroidism during pregnancy, and the fact that this has been demonstrated to be cost effective. When establishing a screening program, normative values should be based preferably on locally developed trimester-based reference ranges. It would be necessary to implement a specific and simple training program aimed at primary care physicians, obstetricians, internists, and endocrinologists who may be unfamiliar with the TD during pregnancy, with the goal of achieving a correct interpretation of test results before starting treatment. In the future, initiation of universal screening programs for TD in pregnant women will provide the opportunity to evaluate its efficacy, cost-effectiveness, and feasibility, thus confirming its usefulness for achieving a healthier condition for the citizens of tomorrow.

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