

2014 European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children

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Key Words

Pregnancy · Hypothyroidism · Subclinical · Child · Screening · Iodine · Management

Abstract

This guideline has been produced as the official statement of the European Thyroid Association guideline committee. Subclinical hypothyroidism (SCH) in pregnancy is defined as a thyroid-stimulating hormone (TSH) level above the pregnancy-related reference range with a normal serum thyroxine concentration. Isolated hypothyroxinaemia (defined as a thyroxine level below the 2.5th centile of the pregnancy-related reference range with a normal TSH level) is also recognized in pregnancy. In the majority of SCH the cause is autoimmune thyroiditis but may also be due to iodine deficiency. The cause of isolated hypothyroxinaemia is usually not apparent, but iodine deficiency may be a factor. SCH and isolated hypothyroxinaemia are both associated with adverse obstetric outcomes. Levothyroxine therapy may ameliorate some of these with SCH but not in isolated hypothyroxinaemia. SCH and isolated hypothyroxinaemia are both associated with neuro-intellectual impairment of the child, but

there is no evidence that maternal levothyroxine therapy improves this outcome. Targeted antenatal screening for thyroid function will miss a substantial percentage of women with thyroid dysfunction. In children SCH (serum TSH concentration >5.5–10 mU/l) normalizes in >70% and persists in the majority of the remaining patients over the subsequent 5 years, but rarely worsens. There is a lack of studies examining the impact of SCH on the neuropsychological development of children under the age of 3 years. In older children, the evidence for an association between SCH and impaired neuropsychological development is inconsistent. Good quality studies examining the effect of treatment of SCH in children are lacking.

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Introduction

Subclinical hypothyroidism (SCH) in pregnancy is defined by a serum thyroid-stimulating hormone (TSH) concentration higher than the upper limit of the pregnancy-related reference range associated with a normal se-

rum thyroxine [T_4 ; either total (TT_4) or free (FT_4)] concentration. The serum tri-iodothyronine (T_3) level is normal. It occurs in approximately 2–2.5% of pregnant women [1], although in China the incidence has been reported to be 4.0% [2], in Belgium 6.8% [3] and in Northern Spain as high as 13.7% [4]. This is in contrast to overt hypothyroidism (defined as FT_4 below normal in conjunction with elevated TSH or TSH higher than 10 mU/l irrespective of FT_4 levels) which has a prevalence of around 0.2–0.5% in pregnancy and which will not be considered further in this guideline. In children the prevalence of SCH is less than 2% [5]. When considering SCH, it was agreed that the so-called isolated hypothyroxinaemia as a separate entity should also be included in the discussion. This is normally defined as a serum T_4 concentration (TT_4 or FT_4) as being in the lower 2.5% of the reference range [6]. This definition implies that hypothyroxinaemia is associated with a normal TSH concentration.

During the last 2 decades advances in our understanding of thyroid physiology in pregnancy have led to the appreciation of the adverse effects of SCH on both the mother and child. Furthermore, considerable variation in the management of SCH in pregnancy was observed in a recent European Thyroid Association survey [7]. Hence the European Thyroid Association commissioned a task force to prepare the current guidelines. In addition, there have never been any published guidelines on SCH in children. The present guideline may usefully be read in conjunction with guidelines on the management of SCH in non-pregnant persons recently published by Pearce et al. [8] in addition to published guidelines of the American Thyroid Association [6] and the American Endocrine Society [9] both addressing the subject of thyroid and pregnancy.

Methods

The executive committee of the European Thyroid Association and the guideline board nominated a task force for the development of guidelines on the management of SCH in pregnancy and children. The task force had no commercial support, and the members declared no conflict of interest. A list of all relevant topics related to SCH in pregnancy and children was created, and the members then performed a comprehensive literature review, carrying out a systematic Pubmed and Medline search for original and review articles published from 1970 to December 2013. The search terms used were TSH, levothyroxine, pregnancy, SCH, adverse effects, abortion, miscarriage, iodine, thyroid antibodies, children and Hashimoto's disease. The guidelines were constructed based on the best scientific evidence and the skills of the task force. Where available, data derived from randomized clinical trials

(RCT) rather than observational studies has been selected for recommendations. The GRADE system is employed which has been used in other guidelines. The quality of the literature concerning each aspect of the statement was graded as high (RCT evidence – level 1), moderate (intervention short of RCT or large observational studies – level 2) or low quality (case series, case reports, expert opinion – level 3) using modified GRADE criteria [10, 11]. The strength of each statement was classified as strong (S, a recommendation) or weak (W, a suggestion; see Recommendations below), depending upon the clinical significance and weight of opinion favouring the statement. Strong recommendations are clinically important best practice and should be applied to most patients in most circumstances. In contrast, weak statements should be considered by the clinician and will be applicable best practice only to certain patients or under certain circumstances.

Diagnosis of SCH in Pregnancy

SCH can only be diagnosed on the basis of laboratory test results as the symptoms of both SCH and hypothyroidism are non-specific and mimic symptoms that can be associated with variations in lifestyle or those of many other conditions, like pregnancy itself [12].

The diagnosis of primary hypothyroidism during pregnancy is based upon finding of an elevated serum TSH concentration, defined using trimester-specific TSH reference ranges for pregnant women. The reference interval of thyroid function tests in pregnant women differs from that of the general population and among trimesters in the same patient. As the median TSH level is lower in the first trimester of pregnancy when compared with the non-pregnant reference range, the implementation of trimester-specific reference ranges is recommended in order to avoid misclassification of thyroid dysfunction during pregnancy [13].

In areas with sufficient daily iodine intake, the maternal thyroid is stimulated in the first trimester by human chorionic gonadotrophin. The inverse relationship of human chorionic gonadotrophin and TSH levels during early pregnancy has been extensively documented and is particularly evident in the subgroup of women with TSH values at lower centiles [14].

On the base of published studies, mostly from western countries, either the guidelines sponsored by the American Thyroid Association or by the American Endocrine Society suggested the following reference range: first trimester, 0.1 to 2.5 mU/l; second trimester, 0.2 to 3.0 mU/l; third trimester, 0.3 to 3.0–3.5 mU/l [6, 9, 15–17].

It is a matter of discussion whether these reference ranges should be used worldwide. Two studies from China [18, 19] and 1 study from India [20], for example, dem-

onstrated a significantly higher TSH reference range for each trimester; in particular, the study by Li et al. [19] showed that the Chinese population displays 0.12–5.08 mU/l as first trimester reference range; as a consequence, using the suggested 0.1–2.5 mU/l as reference range, about 28% of the pregnant patients in China would suffer from hypothyroidism, versus 4% when using an ethnically specific reference range [6, 21–23]. Further data derived from the 3,944 women participating in the Generation R study demonstrated that a comparison of disease prevalence between a population-based versus an ethnicity-specific reference range changed the diagnosis for 18% of women who were initially diagnosed as having abnormal thyroid function test results [24].

Other than the increase mentioned above in human chorionic gonadotrophin and the downward shift of TSH, pregnancy is also characterized by an increased iodine renal clearance, increased serum T_4 -binding globulin, and inner-ring deiodination of T_3 and T_4 by the placenta. These metabolic changes may also influence the T_4 concentration that appears to be increased during the first trimester and relatively decreased during the second and the third trimesters. Despite the increase in T_4 -binding globulin and the decrease in albumin concentration, some authors maintain that the reliability of the standard immunoassay for FT_4 is satisfactory [25] while others assert its unreliability and emphasize the measurement of FT_4 in the dialysate or ultrafiltrate using online solid phase extraction liquid chromatography tandem mass spectrometry as gold standard [26]. The method is ideally suited for generating reliable, reproducible trimester-specific reference ranges for FT_4 , but unfortunately, this assay technology is labour-intensive, technically demanding, time-consuming and expensive, and it is not readily available in most clinical laboratories.

As the definition of SCH is based on elevated TSH in conjunction with normal FT_4 values, it would be of pivotal importance to establish a universally accepted FT_4 trimester-specific reference range. Available data derived from the literature indicate that in the first trimester the lower FT_4 limit (2.5th percentile) of the reference range, detected by immunoassay, is around 0.80 ng/dl (10.30 pmol/l) [16, 17, 27, 28]. Given the uncertainty in FT_4 measurement during pregnancy, alternative strategies have also been suggested. The first is that the non-pregnant TT_4 range (5–12 µg/dl or 50–150 nmol/l) can be adapted by multiplying this range by 1.5-fold [16]. However, in many laboratories the measurement of TT_4 has been abandoned for a long time; also a TT_4 trimester-specific reference range is lacking. The second is the so-

called FT_4 index that has been indicated as a reliable assay during pregnancy [16]. In this latter case, it should be remembered that this index is a calculated ratio, based on 2 estimates (estimate of T_3 resin uptake and immunoassay estimate of TT_4), both prone to inaccuracy; moreover, no trimester-specific reference intervals are available for the FT_4 index, and finally, the FT_4 index is rarely available [24].

In developing countries the most frequent cause of hypothyroidism is represented by severe iodine deficiency, while in developed countries it is by chronic autoimmune thyroiditis (CAT). Thyroid auto-antibodies are detected in about 50% of pregnant women with SCH and in more than 80% with overt hypothyroidism [29]. Hence in patients with SCH the measurement of thyroid peroxidase antibodies (TPOAb) is recommended to establish if the woman has thyroid autoimmunity [30]. Although in the general population only positive TPOAb tests have been shown to be significantly associated with hypothyroidism, the measurement of thyroglobulin antibodies (TgAb) should not be disregarded. In a study involving 992 unselected women consulting a tertiary referral centre for reproductive medicine, the prevalence of thyroid autoimmunity was 16%; in 8% both types of antibodies were present, in 5% of women isolated positive TgAb were found and 4% had isolated positive TPOAb; women with isolated TgAb had significantly higher serum TSH levels compared to those in women without thyroid autoimmunity [31]. After the first trimester the test for thyroid antibodies may be negative due to the immune suppression seen in pregnancy; in the presence of elevated TSH values and negative thyroid antibodies, thyroid ultrasonography may be helpful in detecting abnormal thyroid texture and subsequent diagnosis [32].

Recommendations

- 1 Trimester-specific reference ranges for TSH and T_4 (total or free) should be established in each antenatal hospital setting. Local variations may occur. (2S)
- 2 If TSH trimester-specific reference ranges are not available in that laboratory, the following reference range upper limits are recommended: first trimester, 2.5 mU/l; second trimester, 3.0 mU/l; third trimester, 3.5 mU/l. (2W)
- 3 TT_4 and FT_4 assays are both suitable for thyroid function testing in pregnancy. (2S)
- 4 TSH should be measured at the beginning of pregnancy if screening is performed. If TSH is elevated, FT_4 and TPOAb should be determined. This will enable SCH or overt hypothyroidism to be diagnosed,

in addition to identifying patients with isolated hypothyroxinaemia as well as central hypothyroidism. (1S)

- 5 In the case of elevated TSH and negative TPOAb, TgAb should be measured. Thyroid ultrasound may be performed to evaluate hypo-echogenicity or an inhomogeneous echo pattern. (2S)

The Role of Iodine in SCH

In pregnancy there is about a 50% increase in iodine requirement to achieve a dietary intake of 250 µg/day. This increase is due to: an increased glomerular filtration and renal iodine clearance as well as iodine transplacental transfer to the fetus, particularly in later gestation [33]. In chronically iodine-deficient pregnant women, depleted iodine thyroid stores are not able to compensate for increased demands; if deficiency is not corrected, it may result in goitre formation and maternal hypothyroidism [34].

In 2011, 393 million Europeans (44.2%), including pregnant women and those of child-bearing age, were estimated to be iodine deficient [35]. Although the situation is slowly improving [36], inadequate iodine intake, particularly in populations at risk, may be observed even in high-income countries traditionally considered to be iodine sufficient [35–39]. For example, assessment of the thyroid status of pregnant women living in Northern Spain revealed that only 14.4% of women in the first trimester and 26.8% in the second trimester had optimal iodine nutrition defined as urinary iodine concentrations (UIC) between 150 and 249 µg/l [4].

The contribution of iodine deficiency to the incidence of SCH and isolated hypothyroxinaemia is variable, depending at least on the degree of iodine deficiency and the incidence of thyroid antibodies. The latter would be associated with SCH independently of iodine deficiency. The Spanish study did show SCH in an iodine-deficient area [4]. An elevated body mass index (BMI) increases the risk of isolated hypothyroxinaemia in iodine-deficient first trimester women [40], and the high prevalence of thyroid disorders including SCH in pregnancy in Belgium has been noted [3].

The deleterious effects of severe iodine deficiency on fetal development have been extensively studied. The introduction of any form of iodine prophylaxis in such cases decreases infant mortality and improves psychoneurological development. The actual adverse effects of mild to moderate iodine deficiency and the benefits resulting

from its correction have been less intensively evaluated. However, there are data suggesting improved motor and cognitive function in children born to mothers with adequate iodine intake, particularly if that status is achieved in pre-pregnancy or early pregnancy [41, 42]. Iodine supplementation during pregnancy (iodized salt vs. iodine supplements) may not influence postnatal child development [43], although supplementation in areas of mild iodine deficiency may also be beneficial [44].

Iodine prophylaxis in subclinically hypothyroid pregnant women has not been studied. Several observational studies in areas with adequate or high iodine intake suggest that there is an increase in the incidence of thyroid autoimmunity. Moreover, intervention studies suggest that increased iodine intake may enhance thyroid autoimmunity as well [45]. However, not all studies generated the same findings, probably because of genetic, racial and environmental differences. It seems that autoimmune exacerbation is a transient phenomenon [46]. Prevention of endemic goitre (and presumably some cases of SCH) can be affected by iodine supplementation in pregnancy [47].

According to the WHO, pregnant and lactating women should be provided with 250 µg iodine daily [48]. This may be achieved by administering iodine supplements containing 150–250 µg of iodine in the form of potassium iodide often as prenatal and pregnancy vitamin supplements. Adequate iodine intake during pregnancy (250 µg of iodine daily) should be preferably achieved before conception. In countries with successful salt iodization programmes, pregnancy-desiring women should be additionally supplemented with 50 µg of iodine [49]. The daily intake of iodine should not exceed 500 µg.

Whether iodine administration will prevent SCH in iodine-deficient women is not clear. The data on TSH levels and iodine nutrition in pregnancy are conflicting. Some studies failed to recognize any significant relation between TSH and iodine status, most frequently assessed with UIC [50, 51]. A positive correlation between TSH level and UIC has also been reported [52]. Excessive iodine intake is even considered a risk factor for SCH (odds ratio, OR, of 6.2 for SCH in Chinese pregnant women with UIC >250 µg/l) [53]; the higher TSH levels in these iodine-supplemented women were attributed to the stunning effect of a sudden increase in micronutrient consumption in populations living in areas of mild to moderate iodine deficiency.

In view of the changing iodine nutrition status of the European population, the international monitoring programme should be conducted on a regular basis.

Recommendations

- 6 The daily iodine intake during pregnancy and lactation should be at least 250 µg and should not exceed 500 µg. (1S)
- 7 A sufficient iodine intake is usually provided by supplementing euthyroid pregnant and lactating women with formulas containing 150 µg of iodine/day, ideally before conception. (1S)
- 8 The effectiveness and side effects of iodine prophylaxis together with or without levothyroxine therapy in subclinically hypothyroid women should be assessed. (3S)

Adverse Effects of SCH on Mother and Child

Maternal Effects

Overt hypothyroidism during pregnancy has been clearly associated with adverse events (pre-eclampsia, gestational hypertension, cretinism, fetal deaths and spontaneous abortion) [54]. Less clear is the association between obstetric complications and SCH. Studies investigating this issue have shown conflicting results. The evaluation of the influence of SCH on pregnancy outcome is currently hampered by the paucity of RCT showing that SCH directly or indirectly contributes to an increased rate of a specific complication, and that treatment with levothyroxine is able to reduce the rate of such complications. Most are studies of association and meta-analyses, whose results have always to be considered with caution.

Recent reports suggest an increased risk for gestational diabetes in SCH. A retrospective study in the USA analysing the medical records (by the International Classification of Diseases-9 codes) of 223,512 singleton pregnancies found an increased risk for gestational diabetes (OR = 1.57, 99% confidence interval, CI, = 1.33–1.86) in patients with primary hypothyroidism [55]; although in this study no difference in the incidence of gestational diabetes mellitus could be detected between SCH and overt hypothyroidism. Another study involving 1,170 women demonstrated that high TSH and thyroid autoimmunity in early pregnancy were associated with a 4-fold increased risk for gestational diabetes and a 3-fold increased risk for low-birth-weight neonates [56]. Tudela et al. [57] have shown that the higher the TSH, the higher the risk of developing gestational diabetes (the predicted percentage of gestational diabetes increased from 1.9 to 4.9% as thyrotropin increased from 0.001 to 10 mU/l; $p = 0.001$). The association between SCH and gestational diabetes mellitus is also supported by a recent meta-analysis [58].

Several studies have confirmed the association of SCH with pregnancy loss. Allan et al. [29] showed that fetal death is significantly more frequent when TSH is higher than 6.0 mU/l (3.8 vs. 0.9%); Benhadi et al. [59] reported a significantly higher mean TSH in women who experienced child loss compared with successful pregnancies (1.48 vs. 1.11 mU/l), and that the incidence of child loss increased by 60% for every doubling in TSH concentration. A comparison of the TSH at 11–13 weeks in women who suffered fetal death versus those who did not found an increase in TSH multiple of the median (MoM; 1.133 vs. 1.007 MoM), and a decrease in FT₄ MoM (0.958 vs. 0.992 MoM) [60]. Negro et al. [61] observed a significant increase in miscarriage rate in TPOAb– women with first trimester TSH 2.5–5.0 mU/l versus <2.5 mU/l (6.1 vs. 3.6%); SCH and thyroid autoimmunity were independently associated with very early embryo loss in 216 women [62]. An increased risk for miscarriage in women with untreated hypothyroidism compared with euthyroid controls (OR = 5.78, 95% CI = 2.4–14) was confirmed in a prospective study [60] but not in a retrospective study where 240 SCH patients showed no difference in miscarriage rate when compared with 10,518 controls (OR = 0.69, 95% CI = 0.10–5.0) [63].

SCH is also associated with gestational hypertension and pre-eclampsia. A study of 68 hypothyroid women found that gestational hypertension was significantly more common in both overt hypothyroidism and SCH patients than in the general population, with rates of 22, 15 and 7.6%, respectively [64]. A retrospective study of pregnancy outcomes in 24,883 women found hypertension in pregnancy in 10.9% of SCH and 8.5% in euthyroid patients, with a significant association between SCH and severe pre-eclampsia [65]. A meta-analysis [66] found a significantly increased risk of pre-eclampsia in patients with SCH (OR = 1.7, 95% CI = 1.1–2.6) but no association between SCH and pregnancy-induced hypertension (OR = 1.00, 95% CI = 0.79–1.29). Confirmation of an increased risk of pre-eclampsia, superimposed pre-eclampsia and preterm birth in primary hypothyroidism has recently been obtained [55].

Although positive thyroid antibodies seem to be significantly associated with the risk of preterm delivery (OR = 1.9, 95% CI = 1.1–3.5), this was not the case with SCH (OR = 1.0, 95% CI = 0.59–1.8) [67]. A report of 404 women with SCH showed a doubled rate of preterm birth with respect to controls [67], and a 3-fold increased rate of preterm deliveries in subclinically hypothyroid women was shown in a Chinese study of 1,000 women [2]. A study involving 5,971 pregnant women showed that those

with a TSH >97.5th percentile had an increased risk of premature and very premature delivery. However, a TSH >97.5th centile was not associated with premature delivery or very premature delivery after the exclusion of TPOAb+ women or comorbidities [68].

Other complications confirmed by some and denied by others are placental abruption, perinatal mortality, admission to the neonatal intensive care unit, low Apgar score and low birth weight [29, 56, 63, 67, 69]; no increased risk was found for high birth weight, congenital malformations and respiratory distress syndrome [29, 63, 67, 69].

Isolated hypothyroxinaemia (normal TSH values with FT₄ below the 5th centile) has been investigated in relation to adverse obstetric events. Casey et al. [70] diagnosed first trimester isolated hypothyroxinaemia (FT₄ <0.86 ng/dl) in 233/17,298 (1.3%) with no excessive adverse pregnancy outcomes. In 10,990 patients first trimester hypothyroxinaemia was associated with preterm labour (adjusted OR = 1.62; 95% CI = 1.00–2.62) and macrosomia (adjusted OR = 1.97; 95% CI = 1.37–2.83), while in the second trimester, it was associated with gestational diabetes (adjusted OR = 1.7; 95% CI = 1.02–2.84) [64]. The median FT₄ MoM was reduced in women with preterm delivery compared to control (0.94 vs. 0.99, $p < 0.001$) [60]; in another study, isolated hypothyroxinaemia was related to fetal distress, small for gestational age and musculoskeletal malformations [2]. Korevaar et al. [68] noted that 1.4% of pregnant women were hypothyroxinaemic (FT₄ <2.5th percentile) and had a 2.5-fold increased risk of premature delivery and a 3.6-fold increased risk of very premature delivery. Similar significant results were found when all women with low FT₄ levels were analysed irrespective of their TSH, as well as after the exclusion of TPOAb+ women or those with comorbidities.

Childhood Effects

Several studies have assessed the association between maternal SCH in pregnancy and neuropsychological development of the offspring. Haddow et al. [71] analysed TSH in stored sera from over 25,000 women in the second trimester. Sixty-two women had elevated TSH; of these, 48 were not taking T₄ during the pregnancy. The mean IQ of the children born to the 48 women with high TSH and not on T₄ was 7 points lower than that of 124 control children born to women who had normal TSH levels during the pregnancy ($p = 0.005$). It is noteworthy that the study did not classify overt hypothyroidism and SCH, and some of the women with high TSH had overt hypo-

thyroidism. Consistently with these results, in a prospective cohort study of 1,017 pregnant women from China, Su et al. [2] found an association between SCH in early pregnancy (before 20 weeks of gestation) and impaired visual development (OR = 12.14, 95% CI = 1.22–120.70) and neurodevelopmental delay (OR = 10.49, 95% CI = 1.01–119.19). A retrospective Chinese study also supports the association between maternal SCH in pregnancy and impaired neuropsychological development, although only 18 women with SCH were included [72].

In contrast, a recent cohort study from the Netherlands, which included 3,659 children and their mothers, did not find an association between maternal TSH in early pregnancy and offspring cognitive development at 18 and 30 months [28]; in a separate study, the same group did find an association between increasing maternal TSH in early pregnancy and behavioural problems in their offspring [73]. A population-based cohort study of 1,761 children and their mothers from Spain also failed to show an association between maternal TSH levels in pregnancy and neuropsychological development in the children [74]. Another small study found a similar mean IQ in 19 children born to women with SCH in pregnancy due to inadequate levothyroxine replacement and 19 control children whose mothers were euthyroid [75].

Several studies, but not all, have also shown an association between maternal hypothyroxinaemia and impaired neuropsychological development of the offspring. Pop et al. [76, 77] found that children born to women with FT₄ below the 10th percentile in early pregnancy have impaired psychomotor development. This association between maternal hypothyroxinaemia and impaired neuropsychological development of the offspring is supported by further case-control and population-based cohort studies [28, 74, 78–80]. Furthermore, maternal hypothyroxinaemia has also been shown to be associated with attention-deficit/hyperactivity disorders [81] and autism in children [82]. In contrast, other studies have failed to confirm the association between maternal hypothyroxinaemia and neuropsychological development of the offspring [83–85].

Conclusions

- Current data indicate an increase in pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia and preterm delivery in women with SCH in pregnancy.
- The association between SCH in pregnancy and impaired neuropsychological development of the offspring is inconsistent.

- Maternal hypothyroxinaemia is associated with impaired neuropsychological development of the offspring.

Recommendation

- 9 Further studies are required to determine the precise effects of SCH on obstetric outcome in addition to their effects on childhood neuro-intellectual development. (2S)

Effects of Treatment of SCH and IH with Levothyroxine

The debate about substitution therapy in SCH is still open both for non-pregnant and pregnant patients. The background of this debate relates to association studies which show detrimental effects of SCH on the course of pregnancy and on the IQ of children born from hypothyroid mothers. Since results on cognitive testing of children <3 years of age do not predict future development, long-term data are needed.

A prospective, randomized trial of 984 unselected women with first trimester TSH of 0.3–4.2 mU/l, admittedly not subclinically hypothyroid, demonstrated that TPOAb+ patients treated with levothyroxine had a miscarriage rate lower than untreated ones (3.5 vs. 13.8%), and similar to that of TPOAb– ones (2.4%) [86]. A significant increase in preterm deliveries in TPOAb+ women was also reduced in TPOAb+ patients treated with levothyroxine [86]. As patients with thyroid antibodies are more likely to develop SCH during gestation, this study is relevant to a possible therapy of SCH. A randomized control trial has shown that levothyroxine treatment decreased the occurrence of adverse events in the mother and fetus in women who were TPOAb+ and who had a circulating baseline TSH level >2.5 mU/l during the first trimester of pregnancy [69]. A recent prospective study from Belgium found the same reduction in miscarriage rate when treating TPOAb+ women with TSH >1 mU/l with 50 µg of levothyroxine [87].

To date, only 1 single prospective RCT has assessed the effect of levothyroxine therapy for mild maternal thyroid failure during pregnancy on offspring IQ. Lazarus et al. [88] randomized mildly hypothyroid pregnant women to levothyroxine treatment versus no treatment. At the age of 3, children of women treated with levothyroxine (started at a median gestational age of 13 weeks) had IQ tests which did not differ from the children of untreated women.

Levothyroxine treatment of SCH would appear to have the potential benefits which outweigh the potential risks. The question as to whether levothyroxine therapy is indicated for euthyroid women with positive thyroid antibodies is beyond the scope of this guideline.

Several ongoing studies will tell us whether or not the suggestion of treating SCH is definitive. A large-scale prospective randomized controlled trial sponsored by the National Institute of Child Health and Human Development (USA) is screening pregnant women with less than 20 weeks gestation for SCH or hypothyroxinaemia, and randomizing to treatment with levothyroxine or placebo until delivery. The offspring will have annual developmental testing done until 5 years old to determine if therapy is effective in improving IQ at 5 years of age. The TABLET (Thyroid Antibodies and Levothyroxine) trial (UK), and the T₄ Life trial (the Netherlands), are two multicentre, placebo-controlled, double-blind studies, designed to assess the impact of levothyroxine treatment (started before conception) on miscarriage and preterm delivery in euthyroid women with thyroid antibodies and investigate multiple immunological markers.

Meanwhile it is reasonable practice to maintain TSH values in women planning pregnancy below 2.5 mU/l, especially in those with positive TPOAb; newly diagnosed patients should be treated in order to normalize maternal serum TSH values within the trimester-specific pregnancy reference range [89].

Despite the pivotal role of T₄ in the neurodevelopment of the fetus, there is no demonstrable effect of maternal levothyroxine treatment on child neurodevelopment in relation to maternal SCH or maternal hypothyroxinaemia.

Recommendations

- 10 SCH arising before conception or during gestation should be treated with levothyroxine. (2S)
- 11 To date, no study of intervention is available to demonstrate a benefit from treating hypothyroxinaemic women in terms of obstetric complications. (1S)
- 12 However, levothyroxine therapy may be considered in isolated hypothyroxinaemia detected in the first trimester because of its association with neuropsychological impairment in children. (3W)
- 13 Levothyroxine therapy is not recommended in isolated hypothyroxinaemia detected in the second to third trimester. (3S)

Practical Management of SCH in Pregnancy

In a hypothyroid patient on substitutive treatment before conception, a 25–50% increase in levothyroxine dosage is required. The amount of levothyroxine increase depends on the aetiology of hypothyroidism, being higher in those with radioiodine- or surgery-induced hypothyroidism [90, 91]. When hypothyroidism is newly discovered during pregnancy, a study suggests initiating the treatment with the following levothyroxine doses: 1.20 µg/kg/day for SCH with TSH ≤4.2 mU/l, 1.42 µg/kg/day with TSH >4.2–10 and 2.33 µg/kg/day for overt hypothyroidism [92]. TSH values should be checked every 4–6 weeks at least during the first trimester and once during the second and third trimesters [93]. The recommended treatment of maternal hypothyroidism is with administration of oral levothyroxine. It is strongly recommended not to use other thyroid preparations such as T₃ or desiccated thyroid, which cause lowering of serum T₄ levels. In patients with morning sickness, the administration of levothyroxine late at night may be a valid option.

The question arises as to what advice regarding levothyroxine therapy should be given to a woman who has been receiving treatment during gestation for SCH. Initially, it would seem reasonable to continue levothyroxine therapy but adjust the dose as it will probably reduce after delivery. However, a recent study [94] of 523 women without known thyroid disease identified 65 (12.4%) with SCH during pregnancy defined as TSH greater than 3 mU/l. Of these, 75.4% had normal thyroid function when studied 5 years after delivery; only 16 (24.6%) had persistent high TSH (TSH >4.5 mU/l after pregnancy) suggesting that the majority of cases of SCH in pregnancy are transient and recover after pregnancy. Women with TPOAb and TSH greater than 5 mU/l in pregnancy were more likely to have persistently elevated TSH.

Recommendations

- 14 The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. The use of levothyroxine-T₃ combinations or desiccated thyroid is not recommended. (1S)
- 15 The goal of levothyroxine treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range. (1S)
- 16 In newly diagnosed patients with SCH in pregnancy, a starting dose of 1.20 µg/kg/day is advised. (2S)
- 17 Women with SCH and those with overt hypothyroidism desiring pregnancy should take levothyroxine in a dose to ensure a TSH level of <2.5 mU/l. (2S)

18 In hypothyroid women already treated with levothyroxine before conception, the amount of increase in levothyroxine may vary from 25 to 50%, depending on the aetiology of hypothyroidism and prepregnancy TSH level. (1S)

19 TSH values should be checked every 4–6 weeks during the first trimester and once during the second and third trimesters, and the levothyroxine dose should be adjusted as necessary to reduce TSH to <2.5 mU/l or within the trimester-specific reference range. (2S)

20 Following delivery the levothyroxine dose should be reduced to the preconception dose. Women diagnosed with SCH during pregnancy with TSH less than 5 mU/l and negative TPOAb could stop levothyroxine after delivery and have thyroid function checked 6 weeks after delivery. (2S)

21 Women diagnosed with SCH during pregnancy should be re-evaluated 6 months and 1 year after delivery to ascertain the continuing requirement for levothyroxine. (2S)

Screening for Thyroid Hypofunction in Pregnancy

Screening is a process of identifying apparently healthy people who are at an increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition [95]. Criteria for screening include the presence of a well-defined medically important disorder with known incidence/prevalence. The screening test should be simple and safe with established cut-off values, and an effective treatment must be available. Adequate logistics for the testing and follow-up must be present, and the cost of test relative to benefit should be known. Most importantly, the test should be acceptable to the patient and be approved by the hospital management [96].

The universal screening of asymptomatic pregnant women for hypothyroidism in the first trimester is controversial. Because of insufficient evidence, and because the criteria for universal screening are not all satisfactory, most professional societies essentially from iodine sufficient countries recommend targeted case finding rather than universal screening. The American Thyroid Association recommends measurement of serum TSH in pregnant women if they are symptomatic, from an area of known moderate to severe iodine insufficiency, or have a family or personal history of thyroid disease, type 1 diabetes, history of miscarriage, preterm delivery, history of

head and neck radiation or morbid obesity (BMI >40) [6]. In the American Endocrine Society guidelines some members recommended screening while others did not [9]. All current recommendations support a targeted screening strategy, but such a strategy may miss at least from 33 to 81% of women with hypothyroidism [97–100].

Therefore some endocrinologists have argued for universal screening for thyroid dysfunction in pregnant women or those planning to become pregnant [29, 97]. However, the only prospective randomized trial undertaken to assess the value of screening in relation to childhood cognitive functional outcome failed to show any benefit of screening in pregnancy [88]. Nevertheless, there is support for screening to prevent pregnancy-associated problems [29, 99, 101] in addition to recognition of post-partum thyroiditis [102]. Despite finding no significant decrease in obstetric complications with universal screening and case finding, Negro et al. [69] showed fewer obstetric complications in the low risk group identified by universal screening and benefiting from hypo/hyperthyroidism treatment. This provides some evidence for universal screening in pregnant women with measurement of TPOAb and TSH. The potential benefit of early thyroid screening was highlighted by a study in which levothyroxine treatment for TPOAb+ pregnant women who were diagnosed via universal screening led to a reduction in miscarriage rates [87]. Moreover, a study evaluating the cost-effectiveness of screening all pregnant women for autoimmune thyroid disease during the first trimester demonstrated a positive cost-benefit compared to no screening [103]. A meta-analysis performed by obstetricians in the Netherlands concluded that the overall lack of evidence precludes a recommendation for universal screening and is only justified in a research setting [104]. Despite a lack of consensus among professional organization guidelines regarding thyroid dysfunction screening, a survey conducted in Maine showed that many practitioners have already implemented routine TSH testing in pregnant women [105]. Recently, a European survey found similar results, with 42% of responders screening all pregnant women for thyroid dysfunction [7]. Results in abstracts presented at the American Thyroid Association meeting in October 2013 showed that 74% of respondents advocated universal thyroid screening with TSH [106]. The Spanish endocrine community also favours universal screening [107]. To date there is limited evidence that levothyroxine treatment of pregnant women with SCH, isolated hypothyroxinaemia or thyroid autoimmunity is beneficial. Therefore, there is ongoing debate regarding the need for universal screen-

ing for thyroid dysfunction during pregnancy [108]. Efforts are still required to provide more high-quality evidence to justify screening. The results of a large randomized study in the USA are awaited. There is some evidence that screening (with levothyroxine intervention therapy) may at least prevent or reduce some obstetric complications associated with SCH in pregnancy [109]. There is also a view that it may be preferable to screen for overt thyroid dysfunction only [110]. Meanwhile, optimal co-operation and communication between endocrinologists and obstetricians is also necessary.

Conclusions

- Evidence for screening for SCH in pregnancy is equivocal.
- The decision regarding screening for SCH must be reconsidered when new high-quality evidence becomes available.
- There is no evidence that screening specifically for isolated hypothyroxinaemia is indicated.

Recommendations

- 22 Despite the beneficial effects of levothyroxine treatment on obstetric outcome and the fact that the previously recommended targeted approach to screening thyroid function will miss a large percentage of women with thyroid dysfunction, we do not recommend universal screening for SCH because of the lack of grade 1 evidence. (2S)
- 23 Note: although there are still no well-controlled studies to justify universal screening, the majority of the authors (C.D., A.H.-D., J.L., R.N.) recommend universal screening because of the beneficial effects of levothyroxine treatment on unknown overt hypothyroidism, on obstetric outcome and the fact that the targeted approach will miss a large percentage of women with SCH, especially in mildly iodine-deficient women. (2W)

SCH in Childhood

Diagnosis and Causes of SCH in Children

Dynamic changes in thyroid function occur following delivery in the newborn infant, but a serum TSH concentration >5 mU/l can be considered to be abnormal after 1 month of age when modern third-generation assays are used [111, 112]. Thereafter, both the serum TSH and thyroid hormone levels continue to decline gradually to values more typical of the adult. Because the serum FT₄ con-

centration is somewhat higher in the young, optimally age-related normative values for the assay in use should be employed, though these are not always available. The definition of SCH varies widely among different studies, with some restricting the definition to a slightly elevated value using a serum TSH concentration (e.g. anywhere between 5 and 10 mU/l), associated with an age-appropriate normal TT₄ or FT₄ concentration, whereas others use a much less stringent definition without any upper TSH limit.

In addition to normative values, infants and children differ from adults in the causes and, therefore, the natural history of the thyroid dysfunction, as well as the consequences. Unique to infancy and childhood, thyroid hormone has important, age-dependent maturational effects on brain development, especially in the first 3 years of life, whereas effects on linear growth persist until epiphyseal closure in adolescence [113]. The thyroid gland in infancy and childhood is also particularly susceptible to the effects of ionizing radiation [114, 115]. Clearly a decision about whether or not to treat a child with SCH will depend not only on the potential for adverse effects but also on the likelihood that the SCH will worsen. In general, in iodine-sufficient areas of the world SCH in younger children is more likely to be idiopathic or related to a diverse array of perinatal and genetic causes, whereas thyroid autoimmunity is increasingly common in older children and adolescents.

Natural History of SCH in Childhood and Adolescence General Population

Lazar et al. [116] reported the outcome of mild TSH elevation in 121,052 children in a single health care organization in Israel in whom thyroid function tests were ordered. Of 2.9% of children in whom the initial serum TSH concentration was >5.5–10 mU/l, the subsequent value obtained an average of 2 months later was normal in 73.6% and mildly abnormal in approximately 20%, with a tendency to normalize in those who were retested over the subsequent 5 years. If the initial serum TSH concentration was >10 mU/l, subsequent normalization was observed in only 40% of patients. Those whose initial serum TSH concentration was >5.5–10 mU/l, 8.5% were treated, though the reasons for therapy were not defined. Antithyroid antibodies were measured in just 20% of the patients, and further clinical information was not available. The only predictive factors of likelihood to progress were an initial serum TSH concentration >7.5 mU/l and female gender, but not the age of the patient.

'Persistent Hyperthyrotropinaemia' and Non-Autoimmune ('Idiopathic') SCH

A mild elevation in the serum TSH concentration on newborn screening has been detected with increased frequency in recent years [117], due, in part, to the increased stringency of the criteria used for diagnosis of congenital hypothyroidism [118, 119]. The finding is more common in children born premature [120], small for gestational age [121] and after in vitro fertilization [122] as well as in those with trisomy 21 [123]. In a small proportion of cases a mild morphological abnormality in thyroid gland development [124] or genetic defect in thyroid hormoneogenesis has been demonstrated, the latter including mutations in the genes for the TSH receptor [124–126], dual oxidase 2 [127] and thyroid peroxidase [124]. While many such cases represent transient abnormalities, in a proportion of cases the SCH persists.

A study identified 16 cases of 'transient hyperthyrotropinaemia' amongst 281,468 Japanese newborn babies screened, an incidence of 1 in 17,600 [128]. Transient hyperthyrotropinaemia was defined as an initial serum TSH concentration >4 standard deviations above the normal mean (equivalent to >17 mU/l, mean value 7.4 mU/l). The FT₄ concentration was normal in all the children studied, and none of the babies had an abnormality of thyroid gland development on imaging or heterophile antibodies that might have interfered with the assay for TSH. After 2–7 years of follow-up, the serum TSH concentration normalized in 14 cases, and worsened in 2 despite an initial normalization within the first year of life. Three of the children developed a goitre.

Daliva et al. [129] studied 14 American infants with mild hypothyroidism detected on newborn screening. Whereas the initial filter paper T₄ concentration was abnormal in 2 cases, the confirmatory serum FT₄ or T₄ concentration was normal in 13 babies, associated with a median serum TSH level of 8.4 mU/l (normal <4.6 mU/l). All 14 babies were treated, and thyroid hormone replacement was withdrawn when the babies were approximately 3 years of age. On retesting 1–6 months later, the serum TSH concentration normalized in 5 of the babies and remained mildly abnormal (5–11 mU/l) in 9.

A study of 56 children with a 'false-positive' result on newborn screening found that 50% had SCH at 16–44 months of age [124]. In a follow-up study of 44 of these children at an average age of 5.3 years (range 4.1–6.6), SCH persisted in 19 (43.2%) [130]. Children who were euthyroid in early childhood remained euthyroid on re-evaluation, though the mean TSH concentration was significantly higher than that of the control group. At 8 years

Table 1. Outcome of SCH due to chronic autoimmune thyroiditis in childhood

Authors	Study design	Location	Number	Initial TSH, mU/l	TSH ref. range, mU/l	Follow-up, years	Outcome		
							↑TSH/OH	SCH	euthyroid
<i>Initial TSH ≤20 mU/l</i>									
Moore [134]	R	USA	18 (7)	19.1 (5.2–64)	0.6–5.0	5.8 (1–1.8)	1 (5.6)	10 (55.6)	7 (38.9)
Wang et al. [135]	P	Taiwan	15	>5–<20	>5	6.4±3.9	4 (26.7)	3 (20)	8 (53.3)
Gopalakrishnan et al. [136]	P	India	32	10.95 (6.8–18.7)	0.25–5.0	>2	4 (12.5)	21 (65.6)	7 (21.9)
Fava et al. [137]	R/P	Italy	14	9.3±3.7	<5.0	4.7(2.8–12.4)	1 (7.1)	10 (71.4)	3 (21.4)
Subtotal			79	≤20		4.7	10 (12.9)	44 (53.2)	25 (33.9)
<i>Initial TSH ≤12 mU/l</i>									
Radetti et al. [138]	R/P	Italy	55	>8.8–10	<4.2–5.0	4.9 (0.1–32.6)	23 (41.8)	16 (29.1)	16 (29.1)
Demirbilek et al. [139]		Turkey	29	8.0 (6.2–11.6)	n.a.	3.4 (1.8–6)	11 (37.9)	9 (31)	9 (31)
Radetti et al. [140]		Italy	87	>8.8–10	<4.2–5.0	3	34 (39.1)	17 (19.5)	36 (41.4)
Subtotal			171	≤12		3.8	68 (39.8)	42 (24.6)	61 (35.7)
Total			250			4.3	78 (31.2)	86 (34.4)	86 (34.4)

Number = Number of patients, with number treated in parentheses; follow-up expressed as median with range in parentheses or mean ± SD; outcome given as number with percentage in parentheses. OH = Overt hypothyroidism; R = retrospective; P = prospective; n.a. = not assessed.

of age, SCH persisted in 14 (31.8%), in 13 of whom a morphological or genetic defect could be demonstrated. None of the children developed overt hypothyroidism.

Wasniewska et al. [131] prospectively evaluated 92 patients (mean age 8.1 ± 3 years) with idiopathic SCH, defined as a serum TSH concentration of 5–10 mU/l, associated with a normal T_4 /FT $_4$ concentration, discovered on routine screening. None of the patients had a history of thyroid irradiation or were on medication known to affect thyroid function, and none had thyroid antibodies detectable in serum or a morphological abnormality of the thyroid gland either on physical examination or on ultrasound. After 2 years' observation, the serum TSH concentration normalized in 38 patients (41%), remained mildly elevated in 43 (47%) and rose to >10 mU/l in 11 (12%) in 2 of whom the TSH increase was accompanied by the detection of TPOAb and findings on thyroid ultrasound consistent with CAT.

Trisomy 21 (Down Syndrome)

SCH is particularly common in children with trisomy 21, the prevalence being estimated as between 25.3 and 60% [for a review, see 123]. In infants and young children this appears to be due to a poorly understood dysregulation of the hypothalamic-pituitary-thyroid axis which tends to normalize in a majority of patients. In 1 recent study of 53 children with trisomy 21 six months to 5 years

of age, the SCH normalized in >70%, with a higher remission rate in patients without a goitre and without detectable thyroid antibodies in serum [132]. In older children and adults, there is an increased risk of CAT (see below).

Chronic Autoimmune Thyroiditis

In older children and adolescents, the most frequent cause of SCH is CAT, a disorder that is more common in certain genetic syndromes (trisomy 21 and Turner syndrome) and in patients with other organ-specific autoimmune diseases (especially type 1 diabetes and coeliac disease) [133].

SCH due to CAT is commonly thought to be benign and remitting in childhood, but analysis of the data is complicated by differences between studies in patient selection, small numbers and a relatively limited duration of follow-up. We evaluated the results of 7 observational studies in different ethnic populations in which the number of subjects was >10 and the follow-up was ≥2 years [134–140]. Overall, of 250 children evaluated for an average duration of 4.3 years, 33.9% became euthyroid; in 41.7% SCH persisted while in 24.4% of children the hypothyroidism worsened. However, the results were heavily influenced by the definition of SCH. We therefore stratified studies according to whether the initial mean serum TSH concentration was ≤20 or ≤12 mU/l (table 1).

Whereas approximately one third of children became euthyroid irrespective of the definition of SCH, the hypothyroidism apparently worsened in a much larger percentage of patients when the definition was limited to a serum TSH concentration <12 mU/l. Since the T₄/FT₄ concentration was not indicated in the latter studies, some of these patients would not have been considered to have worsened in the studies in which a higher TSH cut-off was used. Progression to overt hypothyroidism was associated in some but not all studies with the initial TSH concentration and the presence of a goitre and, in one report, with the coexistence of coeliac disease [140]. Elevated TgAb and TPOAb at diagnosis and an increase in the serum TSH and TPOAb concentration on follow-up were also associated with an increased risk of progression in some but not all studies.

SCH after Irradiation

Children, particularly those <10 years of age, are especially susceptible to the development of both thyroid dysfunction and thyroid cancer following ionizing radiation, whether following therapeutic irradiation (e.g. for childhood cancer) [141, 142] or following environmental exposure (e.g. after the Chernobyl accident) [114, 143]. Of these, the most common outcome is SCH. In 1 study of 142 cancer survivors who had received irradiation during childhood as part of the conditioning regimen prior to bone marrow transplantation, SCH developed in 39 patients (26.5%) 1–10 years later [115]. SCH was significantly more common in those who were <9 years of age at the time of the irradiation than in those who were older, and similar results have been obtained by others. The long-term history of SCH following thyroid irradiation is unknown, but thyroid function has been reported to improve in a proportion of patients on long-term follow-up.

Adverse Effects of SCH in Children

Most children with SCH do not have symptoms of overt hypothyroidism [144, 145].

Effects of SCH on Neuropsychological Development

Whilst it is generally accepted that an optimum thyroid hormone level is critical for brain development in the first 3 years of life, there is lack of high-quality studies examining the effect of SCH on neurodevelopment in this patient group. However, several studies have assessed the association between SCH and neuropsychological development in older children. In the National Health and Nutrition Examination Survey III study, 30 (1.7%) of 1,327 adolescents aged 13–16 years were found to have SCH [5]. Cognitive function, assessed using the Revised Wide

Range Achievement Test and Revised Wechsler Intelligence Scale for Children tools, in these children with SCH was not impaired as compared to euthyroid children in the study. Likewise, verbal, performance and full-scale IQ scores in children with SCH were normal and similar to those of controls [5]. In contrast, a small study found that 11 children with SCH performed poorly in cognitive testing for attention as compared to the normative data [146]. In another study with 17 cases and 17 controls, there was no significant difference in the total intelligence scores between the two groups, but children with SCH performed poorly in tests measuring attention [147].

Effects of SCH on Growth

Three observational studies have examined the association between SCH and short stature in children. In a cohort study of 88 children and adolescents with SCH, 19.3% were found to have idiopathic short stature [126], although this high prevalence may have been due to selection bias. In contrast, a cross-sectional case-control study of 36 children with SCH and 36 healthy euthyroid children matched for age, sex, puberty and socio-economic status did not show an association between SCH and short stature [144]. Furthermore, there was no significant difference in height of the children whose SCH persisted compared to those whose SCH resolved after a follow-up period of 2–9.3 years. Consistent with these findings, there were no significant changes in height of the children with persistent SCH as compared to those whose thyroid function normalized during the 2-year study period [131].

Effects of SCH on BMI, Metabolic Parameters and Cardiovascular Risk

The studies analysing the association between obesity and SCH in children have shown inconsistent results. In a cohort study of 88 children and adolescents with SCH, 28.4% were found to be overweight or obese, although this high prevalence may be due to selection bias [126]. However, a large community-based study has also shown a significantly higher prevalence of SCH in obese children as compared to non-obese children (9 vs. 6.5%) [148]. In another large cohort study of 22,747 children and adolescents with type 1 diabetes, 1,638 (7.2%) were found to have SCH. These children had significantly higher BMI as compared to euthyroid children [149]. In contrast, other studies failed to confirm the association between SCH and obesity [131, 144]. Furthermore, as the TSH level in obese children tends to decrease with weight loss from lifestyle changes [150–152] and levothyroxine treatment in children with

hypothyroidism is associated with minimal change in BMI [153], it is thought that the mildly elevated TSH is the consequence of obesity rather than the cause [154].

A significantly higher concentration of serum total and low-density lipoprotein cholesterol was found in children with SCH as compared to euthyroid children [150]. Likewise, another large cohort study including over 12,000 children and adolescents showed that high serum TSH levels are significantly associated with both systolic and diastolic blood pressure, and increased the risk of hypertension in children (OR = 1.72, 95% CI = 1.15–2.57) but not in adolescents [155]. Finally, in a small case-control study, 34 obese children and adolescents with SCH were found to have significant impairment of diastolic and longitudinal systolic cardiac function on echocardiography as compared to 60 obese children with normal TSH [156].

Effects of SCH on Bone Health

A case-control study with 25 children and adolescents with SCH and 25 age- and sex-matched healthy controls showed no difference in bone mineral density and biochemical markers of bone metabolism in the two groups [157].

Impact of Treatment of SCH in Children

Several studies (mostly non-randomized with small sample size) have examined the effects of treatment of SCH in children. A non-randomized study in 39 children (24 prepubertal and 15 pubertal) presenting with short stature and SCH found improvement in growth velocity with levothyroxine treatment for 1 year [158]. Likewise, an improvement in growth velocity with levothyroxine replacement was also found in prepubertal children with type 1 diabetes and SCH [159]. In contrast, a non-randomized study using levothyroxine treatment in 69 children with SCH (compared to untreated children with SCH) for 2 years showed no significant difference in BMI or height [145].

In a small retrospective case-control study, 13 children with type 1 diabetes with SCH were found to have a significantly increased frequency of symptomatic hypoglycaemia as compared to 31 controls despite similar haemoglobin A_{1c} and total insulin requirement in the two groups [160]. After levothyroxine replacement, the frequency of hypoglycaemic episodes in children with SCH was similar to that in the controls.

In a secondary analysis of pooled data from 3 RCT of dietary iodine supplementation, correction of iodine deficiency (associated with SCH) in children showed an improvement in several metabolic parameters, including re-

duction in serum C peptide, total cholesterol and low-density lipoprotein cholesterol [161].

A small short-term non-randomized study (with only 11 children with SCH and 6–8 weeks of study duration) did not show a benefit of levothyroxine treatment in neurocognitive function [146].

Conclusions

- In the general population, SCH (serum TSH concentration >5.5–10 mU/l) normalizes in >70% of children and adolescents and persists in the majority of the remaining patients over the subsequent 5 years, but rarely worsens.
- Non-autoimmune ‘idiopathic’ SCH, either discovered on newborn screening or later during childhood, is a heterogeneous disorder that normalizes in 58% (range 36–88) of patients or persists, but worsens in approximately 10% after up to 8 years of follow-up.
- SCH is 10 times more common in Down syndrome than in the general population. In younger infants and children with negative thyroid auto-antibodies there is a >70% chance that thyroid function will normalize. In children >8 years of age and in adolescents, SCH is more likely to be due to CAT.
- In SCH due to CAT in children, thyroid function normalizes in approximately 34% of patients, remains stable in 42% and worsens in 24% over 4 years of follow-up, but there is considerable fluctuation in individual patients and the risk of progression depends to a considerable extent on the definition of SCH.
- In obese patients, a serum TSH concentration between 5 and 7 mU/l is likely to be the consequence not the cause of the obesity.
- Most children with SCH do not have symptoms and signs of overt hypothyroidism.
- There is a lack of studies examining the impact of SCH on neuropsychological development of children under the age of 3 years. In older children, the evidence for an association between SCH and impaired neuropsychological development is inconsistent.
- SCH in children is not associated with adverse effects on growth or bone health but may be associated with adverse cardiovascular parameters.
- Good-quality studies examining the effect of treatment of SCH in children are lacking.

Recommendations

- 24 In infants >1 month of age whose serum TSH concentration has failed to normalize, therapy with levothyroxine is recommended until 3 years of age when brain

development is no longer thyroid hormone dependent. At that time a trial off therapy can be performed to determine whether the hypothyroidism was transient or is permanent. (2S)

- 25 If an elevated TSH persists, thyroid imaging is recommended to determine whether a structural abnormality exists and whether, therefore, the SCH is likely to be permanent. Further evaluation to identify a possible genetic abnormality of thyroid hormonogenesis is optional. (1S)
- 26 In children with SCH >3 years of age in whom thyroid auto-antibodies are negative initially, regular monitoring of the serum TSH and TPOAb concentration is indicated. Because of the low risk of progression, monitoring can be performed in 1 year's time, and less frequently thereafter if no worsening is observed. (2S)
- 27 Regular monitoring of thyroid function in patients with trisomy 21 is recommended. For further detail, the reader is referred to specific guidelines on this topic [162, 163]. (2S)
- 28 The risk of progression to overt hypothyroidism appears to be increased in children with SCH due to CAT. Therefore it is suggested that in patients with an elevated TPOAb and/or TgAb concentration at presentation, TSH (\pm TPOAb) be monitored every 6–12 months. More frequent monitoring should be considered in patients whose initial TSH concentration is >10 mU/l in whom a decision has been made not to treat. (2W)
- 29 The decision about whether or not to treat should be made after careful discussion with the parents of the risks and potential benefits of treatment. At present there is insufficient evidence to recommend treatment in the majority of children with SCH in whom the se-

rum TSH concentration is <10 mU/l and in whom the TT₄/FT₄ concentration is normal. (2W)

- 30 Although high-quality studies are lacking as to a causal association of SCH after childhood thyroid irradiation with thyroid cancer, it would appear reasonable to treat individuals in this patient group. (2W)

Concluding Remarks

A majority of recommendations of the current guideline on the management of SCH in pregnancy is consistent with that of the previous guidelines from the American Thyroid Association [6] and the Endocrine Society [9] on the same topic. However, recent advances in the field mean that there are several noticeable differences in the current guideline. For example, the current guideline underlines the importance of ethnic variation in trimester-specific reference ranges for TSH and FT₄, recognizes the utility of testing TgAb to ascertain autoimmunity as the aetiology of SCH in pregnancy, and recommends considering levothyroxine replacement in isolated maternal hypothyroxinaemia in the first trimester. It also emphasizes the use of ultrasound in diagnosis. It is hoped that this guideline will promote the evidence base and contribute in reducing inconsistencies in clinical practice by defining current standards of care in the management of SCH in pregnancy and children.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Lazarus JH: Thyroid function in pregnancy *Br Med Bull* 2011;97:137–148.
- 2 Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, Xu YH, Tao FB: Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab* 2011;96:3234–3241.
- 3 Moreno-Reyes R, Glinoer D, Van Oyen H, Vandevijvere S: High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. *J Clin Endocrinol Metab* 2013;98:3694–3701.
- 4 Aguayo A, Grau G, Vela A, Aniel-Quiroga A, Espada M, Martul P, Castaño L, Rica IJ: Urinary iodine and thyroid function in a population of healthy pregnant women in the North of Spain. *Trace Elem Med Biol* 2013;27:302–306.
- 5 Wu T, Flowers JW, Tudiver F, Wilson JL, Punyasavatsut N: Subclinical thyroid disorders and cognitive performance among adolescents in the United States. *BMC Pediatr* 2006;6:1–6.
- 6 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and Postpartum. Thyroid* 2011;21:1081–1125.
- 7 Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K: Treatment and screening of hypothyroidism in pregnancy: results of a European survey. *Eur J Endocrinol* 2012;166:49–54.

- 8 Pearce S, Brabant G, Duntas L, Monzani F, Peeters R, Razvi S, Wemeau J-L: 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2013;2:215–228.
- 9 De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543–2565.
- 10 Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group: GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
- 11 Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM: A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 2008;93:666–673.
- 12 Canaris GJ, Manowitz NR, Mayor G, Ridgway EC: The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000;160:526–534.
- 13 Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG: Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;105:239–245.
- 14 Krassas GE, Poppe K, Glinoe D: Thyroid function and human reproductive health. *Endocr Rev* 2010;31:702–755.
- 15 Haddow JE, Palomaki GE, McClain MR: Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. *Obstet Gynecol* 2006;107:205–206.
- 16 Soldin OP, Soldin D, Sastoque M: Gestation-specific thyroxine and thyroid stimulating hormone levels in the United States and worldwide. *Ther Drug Monit* 2007;29:553–559.
- 17 Haddow JE, McClain MR, Lambert-Messerlian G, Palomaki GE, Canick JA, Cleary-Goldman J, Malone FD, Porter TF, Nyberg DA, Bernstein P, D'Alton ME; First and Second Trimester Evaluation of Risk for Fetal Aneuploidy Research Consortium: Variability in thyroid-stimulating hormone suppression by human chorionic gonadotropin during early pregnancy. *J Clin Endocrinol Metab* 2008;93:3341–3347.
- 18 Yan YQ, Dong ZL, Dong L, Wang FR, Yang XM, Jin XY, Lin LX, Sun YN, Chen ZP: Trimester and method-specific reference intervals for thyroid tests in pregnant Chinese women: methodology, euthyroid definition and iodine status can influence the setting of reference intervals. *Clin Endocrinol (Oxf)* 2011;74:262–269.
- 19 Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, Li C, Xu B, Bi L, Meng T, Du J, Zhang S, Gao Z, Zhang X, Yang L, Fan C, Teng W: Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab* 2014;99:73–79.
- 20 Marwaha RK, Chopra S, Gopalakrishnan S, Sharma B, Kanwar RS, Sastry A, Singh S: Establishment of reference range for thyroid hormones in normal pregnant Indian women. *Br J Obstet Gynaecol* 2008;115:602–606.
- 21 Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, van der Wal MF, Bonsel GJ: Ethnic differences in TSH but not in free T₄ concentrations or TPO antibodies during pregnancy. *Clin Endocrinol (Oxf)* 2007;66:765–770.
- 22 La'ulu SL, Roberts WL: Second-trimester reference intervals for thyroid tests: the role of ethnicity. *Clin Chem* 2007;53:1658–1664.
- 23 La'ulu SL, Roberts WL: Ethnic differences in first-trimester thyroid reference intervals. Similarly TSH lower in Blacks and Asian than in Hispanics and White population. *Clin Chem* 2011;57:913–915.
- 24 Korevaar TI, Medici M, de Rijke YB, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, Hofman A, Ross AH, Visser EW, Hooijkaas H, Steegers EA, Tiemeier H, Bongers-Schokking JJ, Visser TJ, Peeters RP: Ethnic differences in maternal thyroid parameters during pregnancy: the generation R study. *J Clin Endocrinol Metab* 2013;98:3678–3686.
- 25 Anckaert E, Poppe K, Van Uytanghe K, Schiettecatte J, Foulon W, Thienpont LM: FT₄ immunoassays may display a pattern during pregnancy similar to the equilibrium dialysis ID-LC/tandem MS candidate reference measurement procedure in spite of susceptibility towards binding protein alterations. *Clin Chim Acta* 2010;411:1348–1353.
- 26 Kahric-Janicic N, Soldin SJ, Soldin OP, West T, Gu J, Jonklaas J: Tandem mass spectrometry improves the accuracy of free thyroxine measurements during pregnancy. *Thyroid* 2007;17:303–311.
- 27 Dashe JS, Casey BM, Wells CE, McIntire DD, Byrd EW, Leveno KJ, Cunningham FG: Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. *Obstet Gynecol* 2005;106:753–757.
- 28 Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H: Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010;95:4227–4234.
- 29 Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ: Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 2000;7:127–130.
- 30 Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE: Serum TSH, T₄(4), and thyroid antibodies in the United States population (1988–1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87:489–499.
- 31 Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P, Poppe K: Thyroglobulin antibodies: any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment. *Thyroid* 2013;23:1022–1028.
- 32 Rago T, Chiovato L, Grasso L, Pinchera A, Vitti P: Thyroid ultrasonography as a tool for detecting thyroid autoimmune diseases and predicting thyroid dysfunction in apparently healthy subjects. *J Endocrinol Invest* 2001;24:763–769.
- 33 Glinoe D: The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 2005;71:95–122.
- 34 Vermiglio F, Lo Presti VP, Castagna MG, Violi MA, Moleti M, Finocchiaro MD, Mattina F, Artemisia A, Trimarchi F: Increased risk of maternal thyroid failure with pregnancy progression in an iodine deficient area with major iodine deficiency disorders. *Thyroid* 1999;9:19–24.
- 35 Andersson M, Karumbunathan V, Zimmermann MB: Global iodine status in 2011 and trends over the past decade. *J Nutr* 2012;142:744–750.
- 36 Vila L, Serra-Prat M, de Castro A, Palomera E, Casamitjana R, Legaz G, Barrionuevo C, Muñoz JA, García AJ, Lal-Trehan S, García A, Durán J, Puig-Domingo M: Iodine nutritional status in pregnant women of two historically different iodine-deficient areas of Catalonia, Spain. *Nutrition* 2011;27:1029–1033.
- 37 Kibirige MS, Hutchison S, Owen CJ, Delves HT: Prevalence of maternal dietary iodine insufficiency in the north east of England: implications for the fetus. *Arch Dis Child Fetal Neonatal Ed* 2004;89:F436–F439.
- 38 Vanderpump MP, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K, Franklyn JA; British Thyroid Association UK Iodine Survey Group: Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* 2011;377:2007–2012.
- 39 Brantsæter AL, Abel MH, Haugen M, Meltzer HM: Risk of suboptimal iodine intake in pregnant Norwegian women. *Nutrients* 2013;5:424–440.
- 40 Gowachirapant S, Melse-Boonstra A, Wini-Chagoon P, Zimmermann MB: Overweight increases risk of first trimester hypothyroxinemia in iodine-deficient pregnant women. *Matern Child Nutr* 2014;10:61–71.
- 41 Zimmermann MB: The role of iodine in human growth and development. *Sem Cell Develop Biol* 2011;22:645–652.

- 42 Trumpff C, De Schepper J, Tafforeau J, Van Oyen H, Vanderfaellie J, Vandevijvere S: Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: a review. *J Trace Elements Med Biol* 2013;27:174–183.
- 43 Santiago P, Velasco I, Muela JA, Sánchez B, Martínez J, Rodríguez A, Berrio M, Gutierrez-Repiso C, Carreira M, Moreno A, García-Fuentes E, Soriguer F: Infant neurocognitive development is independent of the use of iodised salt or iodine supplements given during pregnancy. *Br J Nutr* 2013;110:831–839.
- 44 Taylor PN, Okosieme OE, Dayan CM, Lazarus JH: Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur J Endocrinol* 2013;170:R1–R15.
- 45 Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Tong Y, Wang W, Gao T, Li C: Effect of iodine intake on thyroid diseases in China. *N Engl J Med* 2006;354:2783–2793.
- 46 Papanastasiou L, Vatalas IA, Koutras DA, Mastorakos G: Thyroid autoimmunity in the current iodine environment. *Thyroid* 2007;17:729–739.
- 47 Liesenkötter KP, Göpel W, Bogner U, Stach B, Grüters A: Earliest prevention of endemic goiter by iodine supplementation during pregnancy. *Eur J Endocrinol* 1996;134:443–448.
- 48 Andersson M, de Benoist B, Delange F, Zupan J: Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation WHO Secretariat. *Public Health Nutr* 2007;10:1606–1611.
- 49 WHO, Unicef, ICCIDD: Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination. A Guide for Programme Managers, ed 3. Geneva, WHO, 2007.
- 50 Medici M, Ghassabian A, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VW, Visser WE, Hooijkaas H, Hofman A, Steegers EA, Bongers-Schokking JJ, Ross HA, Tiemeier H, Visser TJ, de Rijke YB, Peeters RP: Women with high early pregnancy urinary iodine levels have an increased risk of hyperthyroid newborns: the population-based Generation R study. *Clin Endocrinol (Oxf)* 2014;80:598–606.
- 51 Velasco I, Martín J, Gallego M, Gutiérrez-Repiso C, Santiago P, López-Siguero JP, Mesa EG, Peral JH, Pérez V, García-Fuentes E, Soriguer F: Maternal-fetal thyroid function at the time of birth and its relation with iodine intake. *Thyroid* 2013;23:1619–1626.
- 52 Moleti M, Di Bella B, Giorgianni G, Mancuso A, De Vivo A, Alibrandi A, Trimarchi F, Vermiglio F: Maternal thyroid function in different conditions of iodine nutrition in pregnant women exposed to mild-moderate iodine deficiency: an observational study. *Clin Endocrinol (Oxf)* 2011;74:762–768.
- 53 Sang Z, Wei W, Zhao N, Zhang G, Chen W, Liu H, Shen J, Liu J, Yan Y, Zhang W: Thyroid dysfunction during late gestation is associated with excessive iodine intake in pregnant women. *J Clin Endocrinol Metab* 2012;97:E1363–E1369.
- 54 Stagnaro-Green A: Overt hyperthyroidism and hypothyroidism during pregnancy. *Clin Obstet Gynecol* 2011;54:478–487.
- 55 Männistö T, Mendola P, Grewal J, Xie Y, Chen Z, Laughon SK: Thyroid diseases and adverse pregnancy outcomes in a contemporary US cohort. *J Clin Endocrinol Metab* 2013;98:2725–2733.
- 56 Karakosta P, Alegakis D, Georgiou V, Roumeliotaki T, Fthenou E, Vassilaki M, Boumpas D, Castanas E, Kogevinas M, Chatzi L: Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab* 2012;97:4464–4472.
- 57 Tudela CM, Casey BM, McIntire DD, Cunningham FG: Relationship of subclinical thyroid disease to the incidence of gestational diabetes. *Obstet Gynecol* 2012;119:983–988.
- 58 Konstantinos A, Toulis MD, Stagnaro-Green A, Negro R: Maternal subclinical hypothyroidism and gestational diabetes mellitus: a meta-analysis. *Endocr Pract*, in press.
- 59 Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ: Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009;160:985–991.
- 60 Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH: Maternal thyroid function at 11–13 weeks of gestation and subsequent fetal death. *Thyroid* 2010;20:989–993.
- 61 Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A: Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab* 2010;95:E44–E48.
- 62 De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominicis R, Priolo AM, Vermiglio F: Thyroid function in women found to have early pregnancy loss. *Thyroid* 2010;20:633–637.
- 63 Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, Luthy D, Gross S, Bianchi DW, D'Alton ME: Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008;112:85–92.
- 64 Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH: Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 1994;81:349–353.
- 65 Wilson KL, Casey BM, McIntire DD, Halvorson LM, Cunningham FG: Subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 2012;119:315–320.
- 66 Van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JA, Goddijn M, Bisschop PH: Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2011;17:605–619.
- 67 Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG: Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;105:239–245.
- 68 Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, Edward Visser W, Visser W, de Muinck Keizer-Schrama SM, Hofman A, Ross AH, Hooijkaas H, Tiemeier H, Bongers-Schokking JJ, Jaddoe VW, Visser TJ, Steegers EA, Medici M, Peeters RP: Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R study. *J Clin Endocrinol Metab* 2013;98:4382–4390.
- 69 Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A: Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010;95:1699–1707.
- 70 Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF: Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstet Gynecol* 2007;109:1129–1135.
- 71 Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341:549–555.
- 72 Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T: Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clin Endocrinol (Oxf)* 2010;72:825–829.
- 73 Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, de Muinck Keizer-Schrama SM, Hooijkaas H, Steegers EA, Hofman A, Verhulst FC, van der Ende J, de Rijke YB, Tiemeier H: Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatr Res* 2011;69:454–459.
- 74 Julvez J, Alvarez-Pedrerol M, Rebagliato M, Murcia M, Forn J, Garcia-Esteban R, Lertxundi N, Espada M, Tardón A, Riano Galán I, Sunyer J: Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 2013;24:150–157.

- 75 Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehranidoost M, Azizi F: Subclinical hypothyroidism in pregnancy: intellectual development of offspring. *Thyroid* 2011;21:1143–1147.
- 76 Pop VJ, Kuijpers JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL: Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. *Clin Endocrinol (Oxf)* 1999;50:149–155.
- 77 Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ: Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)* 2003;59:282–288.
- 78 Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ: Neonatal effects of maternal hypothyroxinemia during early pregnancy. *Pediatrics* 2006;117:161–167.
- 79 Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, González-Torga A, de Escobar GM: Delayed neurobehavioral development in children born to pregnant women with mild hypothyroxinemia during the first month of gestation: the importance of early iodine supplementation. *Thyroid* 2009;19:511–519.
- 80 Finken MJ, van Eijdsden M, Loomans EM, Vrijkotte TG, Rotteveel J: Maternal hypothyroxinemia in early pregnancy predicts reduced performance in reaction time tests in 5- to 6-year-old offspring. *J Clin Endocrinol Metab* 2013;98:1417–1426.
- 81 Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F: Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab* 2004;89:6054–6060.
- 82 Román GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H: Association of gestational maternal hypothyroxinemia and increased autism risk. *Ann Neurol* 2013;74:733–742.
- 83 Oken E, Braverman LE, Platek D, Mitchell ML, Lee SL, Pearce E: Neonatal thyroxine, maternal thyroid function, and child cognition. *J Clin Endocrinol Metab* 2009;94:497–503.
- 84 Chevrier J, Harley KG, Kogut K, Holland N, Johnson C, Eskenazi B: Maternal thyroid function during the second half of pregnancy and child neurodevelopment at 6, 12, 24, and 60 months of age. *J Thyroid Res* 2011;2011:426–427.
- 85 Craig WY, Allan WC, Kloza EM, Pulkkinen AJ, Waishren S, Spratt DI, Palomaki GE, Neveux LM, Haddow JE: Mid-gestational maternal free thyroxine concentration and offspring neurocognitive development at age two years. *J Clin Endocrinol Metab* 2012;97:E22–E28.
- 86 Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H: Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 2006;91:2587–2591.
- 87 Lepoutre T, Debiève F, Gruson D, Daumerie C: Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. *Gynecol Obstet Invest* 2012;74:265–273.
- 88 Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ: Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012;366:493–501.
- 89 Abalovich M, Alcaraz G, Kleiman-Rubinshtein J, Pavlove MM, Cornelio C, Levalle O, Gutierrez S: The relationship of preconception thyrotropin levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. *Thyroid* 2010;20:1175–1178.
- 90 Verga U, Bergamaschi S, Cortelazzi D, Ronzoni S, Marconi AM, Beck-Peccoz P: Adjustment of L-T₄ substitutive therapy in pregnant women with subclinical, overt or post-ablative hypothyroidism. *Clin Endocrinol (Oxf)* 2009;70:798–802.
- 91 Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR: Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004;351:241–249.
- 92 Abalovich M, Vázquez A, Alcaraz G, Kitai-grotsky A, Szuman G, Calabrese C, Astarita G, Frydman M, Gutiérrez S: Adequate levothyroxine doses for the treatment of hypothyroidism newly discovered during pregnancy. *Thyroid* 2013;23:1479–1483.
- 93 Yassa L, Marqusee E, Fawcett R, Alexander EK: Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 2010;95:3234–3241.
- 94 Shields BM, Knight BA, Hill AV, Hattersley AT, Vaidya B: Five-year follow-up for women with subclinical hypothyroidism in pregnancy. *J Clin Endocrinol Metab* 2013;98:E1941–E1945.
- 95 Public Health England. <http://www.screening.nhs.uk/screening#fileid9598> (accessed November 7, 2013).
- 96 Wald N, Law M: Medical screening; in Warrell DA, Cox TM, Firth JD (eds): *Oxford Textbook of Medicine*, ed 5. Oxford, Oxford University Press, 2010, pp 94–108.
- 97 Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R: Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007;92:203–207.
- 98 Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilius I, Cepkova J, McGrath C, Maly J: Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. *Eur J Endocrinol* 2010;163:645–650.
- 99 Jiskra J, Bartáková J, Holinka Š, Límanová Z, Springer D, Antoňová M, Telička Z, Potluková E: Low prevalence of clinically high-risk women and pathological thyroid ultrasound among pregnant women positive in universal screening for thyroid disorders. *Exp Clin Endocrinol Diabetes* 2011;119:530–535.
- 100 Wang W, Teng W, Shan Z, Wang S, Li J, Zhu L, Zhou J, Mao J, Yu X, Li J, Chen Y, Xue H, Fan C, Wang H, Zhang H, Li C, Zhou W, Gao B, Shang T, Zhou J, Ding B, Ma Y, Wu Y, Xu H, Liu W: The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. *Eur J Endocrinol* 2011;164:263–268.
- 101 Alexander EK: Here's to you, baby! A step forward in support of universal screening of thyroid function during pregnancy. *J Clin Endocrinol Metab* 2010;95:1575–1577.
- 102 Premawardhana LD, Parkes AB, John R, Harris B, Lazarus JH: Thyroid peroxidase antibodies in early pregnancy: utility for prediction of postpartum thyroid dysfunction and implications for screening. *Thyroid* 2004;14:610–615.
- 103 Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A: Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab* 2012;97:1536–1546.
- 104 Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, Goddijn M: Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 2012;18:360–373.
- 105 Haddow JE, McClain MR, Palomaki GE, Kloza EM, Williams J: Screening for thyroid disorders during pregnancy: results of a survey in Maine. *Am J Obstet Gynecol* 2006;194:471–474.
- 106 Srimatkandada P, Stagnaro-Green A, Pearce EN: The majority of ATA members advocate universal thyroid screening in pregnancy (abstract 107). 83rd Annu Meet Am Thyroid Assoc, 2013, p 108.
- 107 Vila L, Velasco II, González S, Morales F, Sánchez E, Torrejón S, Soldevila B, Stagnaro-Green A, Puig-Domingo ML: Controversies in Endocrinology: On the need of universal thyroid screening in pregnant women. *Eur J Endocrinol* 2013;170:R17–R30.
- 108 Reid SM, Middleton P, Cossich MC, Crowther CA, Bain E: Interventions for clinical and subclinical hypothyroidism pre-pregnancy and during pregnancy. *Cochrane Database Syst Rev* 2013;5:CD007752.

- 109 Chang DLF, Pearce EN: Screening for maternal thyroid dysfunction in pregnancy: a review of the clinical evidence and current guidelines. *J Thyroid Res* 2013;2013:851326.
- 110 Laurberg P, Andersen SL, Pedersen IB, Andersen S, Carlé A: Screening for overt thyroid disease in early pregnancy may be preferable to searching for small aberrations in thyroid function tests. *Clin Endocrinol (Oxf)* 2013;79:297–304.
- 111 Elmlinger MW, Kühnel W, Lambrecht HG, Ranke MB: Reference intervals from birth to adulthood for serum thyroxine (T₄), triiodothyronine (T₃), free T₃, free T₄, thyroxine binding globulin (TBG) and thyrotropin (TSH). *Clin Chem Lab Med* 2001;39:973–979.
- 112 Chaler EA, Fiorenzano R, Chilleli C, Llinares V, Areny G, Herzovich V, Maceiras M, Lazati JM, Mendioroz M, Rivarola MA, Belgorosky A: Age-specific thyroid hormone and thyrotropin reference intervals for a pediatric and adolescent population. *Clin Chem Lab Med* 2012;50:885–890.
- 113 Brown RS: The thyroid; in Brook CGD, Clayton PE, Brown RS (eds): *Brook's Clinical Pediatric Endocrinology*, ed 6. Chichester, Wiley-Blackwell, 2009, pp 250–282.
- 114 Nikiforov Y, Gnepp DR, Fagin JA: Thyroid lesions in children and adolescents after the Chernobyl disaster: implications for the study of radiation tumorigenesis. *J Clin Endocrinol Metab* 1996;81:9–14.
- 115 Ishiguro H, Yasuda Y, Tomita Y, Shinagawa T, Shimizu T, Morimoto T, Hattori K, Matsumoto M, Inoue H, Yabe H, Yabe M, Shinohara O, Kato S: Long-term follow-up of thyroid function in patients who received bone marrow transplantation during childhood and adolescence. *J Clin Endocrinol Metab* 2004;89:5981–5986.
- 116 Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M, Meyerovitch J: Natural history of thyroid function tests over 5 years in a large pediatric cohort. *J Clin Endocrinol Metab* 2009;94:1678–1682.
- 117 Harris KB, Pass KA: Increase in congenital hypothyroidism in New York State and in the United States. *Mol Genet Metab* 2007;91:268–277.
- 118 Deladoëy J, Ruel J, Giguère Y, Van Vliet G: Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective population-based study in Québec. *J Clin Endocrinol Metab* 2011;96:2422–2429.
- 119 LaFranchi SH: Increasing incidence of congenital hypothyroidism: some answers, more questions. *J Clin Endocrinol Metab* 2011;96:2395–2397.
- 120 Radetti G, Fanolla A, Pappalardo L, Gottardi E: Prematurity may be a risk factor for thyroid dysfunction in childhood. *J Clin Endocrinol Metab* 2007;92:155–159.
- 121 Thorpe-Beeston JG, Nicolaides KH, Snijders RJ, Felton CV, McGregor AM: Thyroid function in small for gestational age fetuses. *Obstet Gynecol* 1991;77:701–706.
- 122 Sakka SD, Malamitsi-Puchner A, Loutradis D, Chrousos GP, Kanaka-Gantenbein C: Euthyroid hyperthyrotropinemia in children born after in vitro fertilization. *J Clin Endocrinol Metab* 2009;94:1338–1341.
- 123 King K, O'Gorman C, Gallagher S: Thyroid dysfunction in children with Down syndrome: a literature review. *Ir J Med Sci* 2014;107:118–119.
- 124 Calaciura F, Motta RM, Miscio G, Fichera G, Leonardi D, Carta A, Trischitta V, Tassi V, Sava L, Vigneri RJ: Subclinical hypothyroidism in early childhood: a frequent outcome of transient neonatal hyperthyrotropinemia. *J Clin Endocrinol Metab* 2002;87:3209–3214.
- 125 Nicoletti A, Bal M, De Marco G, Baldazzi L, Agretti P, Menabò S, Ballarini E, Cicognani A, Tonacchera M, Cassio A: Thyrotropin-stimulating hormone receptor gene analysis in pediatric patients with non-autoimmune subclinical hypothyroidism. *J Clin Endocrinol Metab* 2009;94:4187–4194.
- 126 Rapa A, Monzani A, Moia S, Vivenza D, Bellone S, Petri A, Teofoli F, Cassio A, Cesaretti G, Corrias A, de Sanctis V, Di Maio S, Volta C, Wasniewska M, Tatò L, Bona G: Subclinical hypothyroidism in children and adolescents: a wide range of clinical, biochemical, and genetic factors involved. *J Clin Endocrinol Metab* 2009;94:2414–2420.
- 127 De Marco G, Agretti P, Montanelli L, Di Cosmo C, Bagattini B, De Servi M, Ferrarini E, Dimida A, Freitas Ferreira AC, Molinaro A, Ceccarelli C, Brozzi F, Pinchera A, Vitti P, Tonacchera M: Identification and functional analysis of novel dual oxidase 2 (DUOX2) mutations in children with congenital or subclinical hypothyroidism. *J Clin Endocrinol Metab* 2011;96:E1335–E1339.
- 128 Miki K, Nose O, Miyai K, Yabuuchi H, Harada T: Transient infantile hyperthyrotropinaemia. *Arch Dis Child* 1989;64:1177–1182.
- 129 Daliva AL, Linder B, DiMartino-Nardi J, Saenger P: Three-year follow-up of borderline congenital hypothyroidism. *J Pediatr* 2000;136:53–56.
- 130 Leonardi D, Polizzotti N, Carta A, Gelsomino R, Sava L, Vigneri R, Calaciura F: Longitudinal study of thyroid function in children with mild hyperthyrotropinemia at neonatal screening for congenital hypothyroidism. *J Clin Endocrinol Metab* 2008;93:2679–2685.
- 131 Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A, De Luca F: Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. *Eur J Endocrinol* 2009;160:417–421.
- 132 Claret C, Goday A, Benaiges D, Chillarón JJ, Flores JA, Hernandez E, Corretger JM, Cano JF: Subclinical hypothyroidism in the first years of life in patients with Down syndrome. *Pediatr Res* 2013;73:674–678.
- 133 Larizza D, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, Autelli M, Coslovich E, Martinetti M: Celiac disease in children with autoimmune thyroid disease. *J Pediatr* 2001;139:738–740.
- 134 Moore DC: Natural course of 'subclinical' hypothyroidism in childhood and adolescence. *Arch Pediatr Adolesc Med* 1996;150:293–297.
- 135 Wang SY, Tung YC, Tsai WY, Lee JS, Hsiao PH: Long-term outcome of hormonal status in Taiwanese children with Hashimoto's thyroiditis. *Eur J Pediatr* 2006;165:481–483.
- 136 Gopalakrishnan S, Chugh PK, Chhillar M, Ambardar VK, Sahoo M, Sankar R: Goitrous autoimmune thyroiditis in a pediatric population: a longitudinal study. *Pediatrics* 2008;122:e670–e674.
- 137 Fava A, Oliverio R, Giuliano S, Parlato G, Michniewicz A, Indrieri A, Gregnoli A, Belfiore A: Clinical evolution of autoimmune thyroiditis in children and adolescents. *Thyroid* 2009;19:361–367.
- 138 Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S; Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED): The natural history of euthyroid Hashimoto's thyroiditis in children. *J Pediatr* 2006;149:827–832.
- 139 Demirbilek H, Kandemir N, Gonc EN, Ozon A, Alikasifoglu A: Assessment of thyroid function during the long course of Hashimoto's thyroiditis in children and adolescents. *Clin Endocrinol (Oxf)* 2009;71:451–454.
- 140 Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, Salerno M, Cappa M, Baiocchi M, Gastaldi R, Minerba L, Loche S: The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. *Clin Endocrinol (Oxf)* 2012;76:394–398.
- 141 Socié G, Curtis RE, Deeg HJ, Sobocinski KA, Filipovich AH, Travis LB, Sullivan KM, Rowlings PA, Kingma DW, Banks PM, Travis WD, Witherspoon RP, Sanders J, Jaffe ES, Horowitz MM: New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. *J Clin Oncol* 2000;18:348–357.
- 142 Van Dorp W, van Beek RD, Laven JS, Pieters R, de Muinck Keizer-Schrama SM, van den Heuvel-Eibrink MM: Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review. *Hum Reprod Update* 2012;18:12–28.

- 143 Ostroumova E, Brenner A, Oliynyk V, McConnell R, Robbins J, Terekhova G, Zablotska L, Likhtarev I, Bouville A, Shpak V, Markov V, Masnyk I, Ron E, Tronko M, Hatch M: Subclinical hypothyroidism after radioiodine exposure: Ukrainian-American cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident (1998–2000). *Environ Health Perspect* 2009; 117:745–750.
- 144 Cerbone M, Bravaccio C, Capalbo D, Polizzi M, Wasniewska M, Cioffi D, Improda N, Valenzise M, Bruzzese D, De Luca F, Salerno M: Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. *Eur J Endocrinol* 2011;164:591–597.
- 145 Wasniewska M, Corrias A, Aversa T, Valenzise M, Mussa A, De Martino L, Lombardo F, De Luca F, Salerno M: Comparative evaluation of therapy with L-thyroxine versus no treatment in children with idiopathic and mild subclinical hypothyroidism. *Horm Res Paediatr* 2012;77:376–381.
- 146 Aijaz NJ, Flaherty EM, Preston T, Bracken SS, Lane AH, Wilson TA: Neurocognitive function in children with compensated hypothyroidism: lack of short term effects on or off thyroxin. *BMC Endocr Disord* 2006;6: 2.
- 147 Ergür AT, Taner Y, Ata E, Melek E, Bakar EE, Sancak T: Neurocognitive functions in children and adolescents with subclinical hypothyroidism. *J Clin Res Pediatr Endocrinol* 2012;4:21–24.
- 148 Marwaha RK, Tandon N, Garg MK, Ganie MA, Narang A, Mehan N, Bhadra K: Impact of body mass index on thyroid functions in Indian children. *Clin Endocrinol (Oxf)* 2013;79:424–428.
- 149 Denzer C, Karges B, Näke A, Rosenbauer J, Schober E, Schwab KO, Holl RW; DPV Initiative and the BMBF-Competence Network Diabetes Mellitus: Subclinical hypothyroidism and dyslipidemia in children and adolescents with type 1 diabetes mellitus. *Eur J Endocrinol* 2013;168:601–608.
- 150 Reinehr T, Isa A, de Sousa G, Dieffenbach R, Andler W: Thyroid hormones and their relation to weight status. *Horm Res* 2008;70: 51–57.
- 151 Radetti G, Longhi S, Baiocchi M, Cassar W, Buzi F: Changes in lifestyle improve body composition, thyroid function, and structure in obese children. *J Endocrinol Invest* 2012;35:281–285.
- 152 Wolters B, Lass N, Reinehr T: TSH and free triiodothyronine concentrations are associated with weight loss in a lifestyle intervention and weight regain afterwards in obese children. *Eur J Endocrinol* 2013;168:323–329.
- 153 Lomenick JP, El-Sayyid M, Smith WJ: Effect of levo-thyroxine treatment on weight and body mass index in children with acquired hypothyroidism. *J Pediatr* 2008;152:96–100.
- 154 Reinehr T: Thyroid function in the nutritionally obese child and adolescent. *Curr Opin Pediatr* 2011;23:415–420.
- 155 Ittermann T, Thamm M, Wallaschofski H, Rettig R, Völzke H: Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. *J Clin Endocrinol Metab* 2012;97:828–834.
- 156 Brienza C, Grandone A, Di Salvo G, Corona AM, Di Sessa A, Pascotto C, Calabrò R, Toraldo R, Perrone L, Miraglia Del Giudice E: Subclinical hypothyroidism and myocardial function in obese children. *Nutr Metab Cardiovasc Dis* 2013;23:898–902.
- 157 Di Mase R, Cerbone M, Improda N, Esposito A, Capalbo D, Mainolfi C, Santamaria F, Pignata C, Salerno M: Bone health in children with long-term idiopathic subclinical hypothyroidism. *Ital J Pediatr* 2012;38:56.
- 158 Cetinkaya E, Aslan A, Vidinlisian S, Ocal G: Height improvement by L-thyroxine treatment in subclinical hypothyroidism. *Pediatr Int* 2003;45:534–537.
- 159 Chase HP, Garg SK, Cockerham RS, Wilcox WD, Walravens PA: Thyroid hormone replacement and growth of children with subclinical hypothyroidism and diabetes. *Diabet Med* 1990;7:299–303.
- 160 Mohn A, Di Michele S, Di Luzio R, Tumini S, Chiarelli F: The effect of subclinical hypothyroidism on metabolic control in children and adolescents with type 1 diabetes mellitus. *Diabet Med* 2002;19:70–73.
- 161 Zimmermann MB, Aeberli I, Melse-Boonstra A, Grimci L, Bridson J, Chaouki N, Mbhenyane X, Jooste PL: Iodine treatment in children with subclinical hypothyroidism due to chronic iodine deficiency decreases thyrotropin and C-peptide concentrations and improves the lipid profile. *Thyroid* 2009;19:1099–1104.
- 162 Basic medical surveillance essentials for people with Down's syndrome-thyroid disorder. Nottingham, Down's Syndrome Medical Interest Group (DSMIG) UK, 2001.
- 163 American Academy of Pediatrics Committee on Genetics: Health supervision for children with Down syndrome. *Pediatrics* 2011; 128: 393–406.