Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to update the guidelines for the management of thyroid dysfunction during pregnancy and postpartum published previously in 2007. A summary of changes between the 2007 and 2012 version is identified in the Supplemental Data (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Evidence: This evidence-based guideline was developed according to the U.S. Preventive Service Task Force, grading items level A, B, C, D, or I, on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms) as well as the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: The guideline was developed through a series of e-mails, conference calls, and one face-to-face meeting. An initial draft was prepared by the Task Force, with the help of a medical writer, and reviewed and commented on by members of The Endocrine Society, Asia and Oceania Thyroid Association, and the Latin American Thyroid Society. A second draft was reviewed and approved by The Endocrine Society Council. At each stage of review, the Task Force received written comments and incorporated substantive changes.

Conclusions: Practice guidelines are presented for diagnosis and treatment of patients with thyroid-related medical issues just before and during pregnancy and in the postpartum interval. These include evidence-based approaches to assessing the cause of the condition, treating it, and managing hypothyroidism, hyperthyroidism, gestational hyperthyroidism, thyroid autoimmunity, thyroid tumors, iodine nutrition, postpartum thyroiditis, and screening for thyroid disease. Indications and side effects of therapeutic agents used in treatment are also presented. (***J Clin Endocrinol Metab* 97: 2543–2565, 2012)**

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For editorials see pages 2619, 2629, and 2632

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This guideline is also available with CME. Go to http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm for more details.

Abbreviations: ATD, Antithyroid drug; DM, diabetes mellitus; FNA, fine-needle aspiration; GH, gestational hyperthyroidism; hCG, human chorionic gonadotropin; MMI, methimazole; PPD, postpartum depression; PPT, postpartum thyroiditis; PTU, propylthiouracil; RAI, radioactive iodine; RNI, recommended nutrient intake; SCH, subclinical hypothyroidism; TG, thyroglobulin; TPO-Ab−, thyroid peroxidase antibody negative; TPO-Ab+, TPO-Ab positive; TRAb, TSH receptor antibodies; UIC, urinary iodine concentration; UIE, urinary iodine excretion; USI, universal salt iodization.

Summary of Recommendations

1.0. Management of hypothyroidism: maternal and fetal aspects

1.1. We recommend caution in the interpretation of serum free T_4 levels during pregnancy and that each laboratory establish trimester-specific reference ranges for pregnant women if using a free T_4 assay. The nonpregnant total T_4 range (5–12 μg/dl or 50–150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T_4 index ("adjusted T_4") appears to be a reliable assay during pregnancy. U.S. Preventive Service Task Force (USPSTF) recommendation level: B; evidence, fair (GRADE 2|⊕⊕◯◯).

1.2.1. Overt maternal hypothyroidism is known to have serious adverse effects on the fetus. Therefore, maternal hypothyroidism should be avoided. For overt hypothyroidism: USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯).

1.2.2. Subclinical hypothyroidism (SCH; serum TSH concentration above the upper limit of the trimester-specific reference range with a normal free T_4) may be associated with an adverse outcome for both the mother and offspring, as documented in antibody-positive women. In retrospective studies, T_4 treatment improved obstetrical outcome, but it has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T_4 replacement in women with SCH who are thyroid peroxidase antibody positive (TPO-Ab+). For obstetrical outcome: USPSTF recommendation level, B; evidence, fair (2|⊕⊕◯◯); for neurological outcome, USPSTF recommendation level, I; evidence, poor (2|◯◯◯◯). The panel also recommends T_4 replacement in women with SCH who are TPO-Ab negative (TPO-Ab−). For obstetrical outcome: USPSTF recommendation level, C; evidence, fair (2|⊕⊕◯◯); for neurological outcome: USPSTF recommendation level, I; evidence, poor (2|◯◯◯◯).

1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯).

1.2.4. The T_4 dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T_4 dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mIU/liter (in an assay using the International Standard) in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific TSH ranges. Thyroid function tests should be remeasured within 30–40 d and then every 4–6 wk. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored every 4–6 wk for elevation of TSH above the normal range for pregnancy. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕◯).

1.2.7. After delivery, most hypothyroid women need to decrease the T_4 dosage they received during pregnancy to the prepregnancy dose. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

2.0. Management of hyperthyroidism: maternal and fetal aspects

2.1. Management of maternal hyperthyroidism: maternal aspects

2.1.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy and gestational thyrotoxicosis because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by the presence of clinical evidence of autoimmunity, a typical goiter, and presence of TSH receptor antibodies (TRAb). TPO-Ab may be present in either case. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯).

2.1.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, antithyroid drug (ATD) therapy should be either initiated (before pregnancy if possible, and for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T_4 at or just above the upper limit of the nonpregnant reference range, USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯), or to maintain total T_4 at 1.5 times the upper limit of the normal reference range or the free T_4 index in the upper limit of the normal reference range. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).

2.1.3. Propylthiouracil (PTU), if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy because of the possible association of methimazole (MMI) with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. MMI 10 mg is considered to be

approximately equal to 100–150 mg of PTU. Recent analyses reported by the U.S. Food and Drug Administration (FDA) indicate that PTU may rarely be associated with severe liver toxicity. For this reason we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy, including the potential difficulties involved in switching patients from one drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3–4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯).

2.1.4. Subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if: 1) a patient has a severe adverse reaction to ATD therapy; 2) persistently high doses of ATD are required (over 30 mg/d of MMI or 450 mg/d of PTU); or 3) a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯).

2.1.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯).

2.2. Management of maternal hyperthyroidism: fetal aspects

2.2.1. Because thyroid receptor antibodies (thyroid receptor stimulating, binding, or inhibiting antibodies) freely cross the placenta and can stimulate the fetal thyroid, these antibodies should be measured by 22 wk gestational age in mothers with: 1) current Graves' disease; or 2) a history of Graves' disease and treatment with ^{131}I or thyroidectomy before pregnancy; or 3) a previous neonate with Graves' disease; or 4) previously elevated TRAb. Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯).

2.2.2. ^{131}I should not be given to a woman who is or may be pregnant. If inadvertently treated, the patient should be promptly informed of the radiation danger to the fetus, including thyroid destruction if treated after the 12th week of gestation. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯). There are no data for or against recommending termination of pregnancy after ^{131}I exposure. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).

2.2.3. In women with TRAb or thyroid-stimulating Ig elevated at least 2- to 3-fold the normal level and in women treated with ATD, maternal free T_4 and fetal thyroid dysfunction should be screened for during the fetal anatomy ultrasound done in the 18th-22nd week and repeated every 4–6 wk or as clinically indicated. Evidence of fetal thyroid dysfunction could include thyroid enlargement, growth restriction, hydrops, presence of goiter, advanced bone age, tachycardia, or cardiac failure. If fetal hyperthyroidism is diagnosed and thought to endanger the pregnancy, treatment using MMI or PTU should be given with frequent clinical, laboratory, and ultrasound monitoring. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯).

2.2.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical and sonographic data and the information gained would change the treatment. USPSTF recommendation level: B; evidence, fair (2|⊕◯◯◯).

2.2.5. All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD) should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯).

3.0. Gestational hyperemesis and hyperthyroidism

3.1. Thyroid function tests (TSH, total T_4, or free T_4 index, or free T_4) and TRAb should be measured in patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria) and clinical features of hyperthyroidism. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯).

3.2. Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free T_4 do not require ATD treatment. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total T_3 values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement. USPSTF recommendation level: B; evidence, poor (2|⊕◯◯◯).

3.3. Women with hyperemesis gravidarum and diagnosed to have Graves' hyperthyroidism (free T_4 above the reference range or total $T_4 > 150\%$ of top normal pregnancy value, TSH < 0.01 μIU/liter, and presence of TRAb) will require ATD treatment, as clinically necessary. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

4.0. Autoimmune thyroid disease and miscarriage

4.1. A positive association exists between the presence of thyroid antibodies and pregnancy loss. Universal screening for antithyroid antibodies, and possible treatment, cannot be recommended at this time. As of January 2011, only one randomized interventional trial has suggested a decrease in the first trimester miscarriage rate in euthyroid antibody-positive women, but treatment duration was very brief before the outcome of interest. However, because women with elevated anti-TPO antibodies are at increased risk for progression of hypothyroidism, if identified such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯).

5.0. Thyroid nodules and cancer

5.1. Fine-needle aspiration (FNA) cytology should be performed for predominantly solid thyroid nodules larger than 1 cm discovered in pregnancy. Women with nodules 5 mm to 1 cm in size should be considered for FNA if they have a high-risk history or suspicious findings on ultrasound, and women with complex nodules 1.5 to 2 cm or larger should also receive an FNA. During the last weeks of pregnancy, FNA can reasonably be delayed until after delivery. Ultrasound-guided FNA is likely to have an advantage for maximizing adequate sampling. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯).

5.2. When nodules discovered in the first or early second trimester are found to be malignant or highly suspicious on cytopathological analysis, to exhibit rapid growth, or to be accompanied by pathological neck adenopathy, pregnancy need not be interrupted, but surgery should be offered in the second trimester. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease and who prefer to wait until the postpartum period for definitive surgery may be reassured that most well-differentiated thyroid cancers are slow growing and that delaying surgical treatment until soon after delivery is unlikely to change disease-specific survival. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯).

5.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women with a previously treated thyroid cancer, in those with an FNA positive for or suspicious for cancer, or in those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more than low-risk patients from a greater degree of TSH suppression. The free T_4 or total T_4 levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).

5.4. Radioactive iodine (RAI) with ^{131}I should not be given to women who are breastfeeding or for at least 4 wk after nursing has ceased. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Furthermore, pregnancy should be avoided for 6 months to 1 yr in women with thyroid cancer who receive therapeutic RAI doses to ensure stability of thyroid function and confirm remission of thyroid cancer. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯).

6.0. Iodine nutrition during pregnancy

6.1. Women in the childbearing age should have an average iodine intake of 150 μg/d. As long as possible before pregnancy and during pregnancy and breastfeeding, women should increase their daily iodine intake to 250 μg on average. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily recommended nutrient intake (RNI) for iodine, *i.e.* 500 μg iodine per day. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).

6.3. Although not advised as a part of normal clinical practice, the adequacy of the iodine intake during pregnancy can be assessed by measuring urinary iodine concentration (UIC) in a representative cohort of the population. UIC should ideally range between 150 and 250 μg/liter. If there is significant concern, the caregiver should assay TSH and thyroid hormone levels. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.4. To reach the daily recommended nutrient intake for iodine, multiple means must be considered, tailored to the iodine intake level in a given population. Different situations must therefore be distinguished: 1) countries with iodine sufficiency and/or with a well-established universal salt iodization (USI) program; 2) countries without a USI program or with an established USI program where the coverage is known to be only partial; and 3) remote areas with no accessible USI program and difficult socioeconomic conditions. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕).

6.5. We recommend that once-daily prenatal vitamins contain 150–200 μg iodine and that this be in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception. Preparations containing iron supplements should be separated from thyroid hormone administration by at least 4 h. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯).

6.6. We recommend that breastfeeding women maintain a daily intake of 250 μg of iodine to ensure that breast

milk provides 100 μg iodine per day to the infant. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

7.0. Postpartum thyroiditis

7.1. There are insufficient data to recommend screening of all women for postpartum thyroiditis (PPT). USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

7.2. Women known to be TPO-Ab+ should have TSH measured at 6–12 wk gestation and at 6 months postpartum, or as clinically indicated. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

7.3. Because the prevalence of PPT in women with type 1 diabetes, Graves' disease in remission, and chronic viral hepatitis is greater than in the general population, screening by TSH is recommended at 3 and 6 months postpartum. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

7.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period after the episode of PPT. An annual TSH level should be performed in these women. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕○).

7.5. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 mIU/liter and who are not planning a subsequent pregnancy do not necessarily require intervention but should, if untreated, be remonitored in 4–8 wk. When a TSH above the reference range continues, women should be treated with levothyroxine. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

7.6. There is insufficient evidence to conclude whether an association exists between postpartum depression (PPD) and either PPT or thyroid antibody positivity (in women who did not develop PPT). USPSTF recommendation level: I; evidence, poor (2|⊕○○○). However, because hypothyroidism is a potentially reversible cause of depression, women with PPD should be screened for hypothyroidism and appropriately treated. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

8.0. Screening for thyroid dysfunction during pregnancy

8.1a. Universal screening of healthy women for thyroid dysfunction *before* pregnancy is not recommended. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

8.1b. However, caregivers should identify individuals at "high risk" for thyroid illness (see Table 1) on the basis of their medical history, physical exam, or prior biochemical data. When such individuals are identified, prenatal measurement of serum TSH is recommended. If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay. Although no randomized controlled trials are available to guide a response, the committee believes it is appropriate to give low-dose T_4 treatment to bring TSH below 2.5 mIU/liter. This treatment can be discontinued if the woman does not become pregnant or postpartum. USPSTF recommendation level: I; evidence, poor (2|⊕○○○).

8.2a. All women considering pregnancy with known thyroid dysfunction and receiving levothyroxine should be tested for abnormal TSH concentrations *before* pregnancy. USPSTF recommendation level: B; evidence, fair (1|⊕⊕○○).

8.2b. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○).

8.2c. All women receiving levothyroxine should be verbally screened prenatally to assess their understanding of changing levothyroxine requirements after conception. These women should be counseled to contact a physician or medical professional immediately upon a missed menstrual cycle or suspicion of pregnancy to check their serum TSH level. An additional recommendation may be to increase their levothyroxine dose by 30%, which is often two additional tablets per week (nine tablets per week instead of seven tablets), until their serum TSH can be checked. USPSTF recommendation level: B; evidence, fair (2|⊕⊕○○).

8.3a. Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕○○○).

8.3b. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery, progression of hypothyroidism, and PPT. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (1|⊕⊕○○) (see also Section 8.5).

8.4a. The committee could not reach agreement with regard to screening recommendations for all *newly pregnant* women. Two versions are therefore presented.

8.4a1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; evidence, fair (2|⊕⊕○○) (Authors supporting: L.D.G., J.R., J.H.L., N.A., C.J.E.).

8.4a2. Some members recommended neither for nor against universal screening of all pregnant women for TSH

abnormalities at the time of their first visit. These members strongly support aggressive case finding to identify and test high-risk women (Table 1) for elevated TSH concentrations by the ninth week or at the time of their first visit before and during pregnancy, and they recognize that in some situations ascertainment of the individual's risk status may not be feasible. In such cases, and where the local practice environment is appropriate, testing of all women by wk 9 of pregnancy or at the first prenatal visit is reasonable. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯) (Authors supporting: M.A., E.K.A., J.M., L.B., S.S., S.J.M., D.L., R.H.C.).

8.4b. If serum TSH is greater than 2.5 mIU/liter at the time of testing (or > 3.0 mIU/liter in the second trimester), levothyroxine therapy should be instituted. For overt hypothyroidism, USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕); for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯); and for SCH and neurological outcome, USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯).

8.4c. If TSH concentration is 2.5–10 mIU/liter, a starting levothyroxine dose of 50 μg/d or more is recommended. Other thyroid preparations (such as T_3) are not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯).

8.5. Women at high risk for PPT in the postpartum months should be screened via assessment of serum TSH. These high-risk groups include: 1) women known to be TPO-Ab+; 2) women with type 1 diabetes; and 3) women with a prior history of PPT. Screening should occur at 6–12 wk postpartum. Women with Graves' disease who enter remission during pregnancy should be screened for recurrence by TSH assay at 3–6 months. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯) (see also Section 7).

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed thyroid dysfunction during pregnancy a priority area in need of practice guidelines and appointed a task force to formulate evidence-based recommendations. The task force followed the approach of the U.S. Preventive Service Task Force and the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to evaluate the strength of each recommendation and the quality of the evidence. The task force used the best available research evidence to develop the recommendations. In the USPSTF system, the strength of a recommendation is graded A, B, C, D, or I (if insufficient), and evidence is graded good, fair, or poor. In the GRADE system strong recommendations use the number 1, and weak recommendations use the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks,* a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated.

This guideline is concerned with the management of pregnant women who may have a variety of known or undisclosed thyroid conditions, such as hypothyroidism and hyperthyroidism, the presence of thyroid autoantibodies, the presence of nodules, or inadequate iodine nutrition. Pregnancy may affect the course of these thyroid disorders, and conversely, thyroid diseases may affect the course of pregnancy. Moreover, the thyroid disorders (and their management) may affect both the pregnant woman and the developing fetus. Finally, pregnant women may be under the care of multiple health care professionals, including obstetricians, nurse midwives, family practitioners, endocrinologists, and/or internists, making the development of guidelines all the more critical.

An international task force was created under the auspices of The Endocrine Society to review the best evidence in the field and develop evidence-based guidelines, and a report was issued in 2007. Because of advances in the field, the committee was reconvened in 2009. The current task force also includes members of the Asia and Oceania Thyroid Association and the Latin American Thyroid Society.

The task force undertook a review of all material on these topics published in English during the past two decades, or earlier at the working group's discretion. We concentrated on original reports and largely excluded reviews from our references. At present, with the exception of studies on iodide nutrition, only a few prospective, randomized intervention trials have been published in this area. We are aware of large-scale prospective intervention trials that are ongoing. Nevertheless, in the past decade many high-quality studies have modified older dogmas

and profoundly changed the ways in which these patients are managed.

Thyroid problems during pregnancy encompass at least eight different conditions, and we have therefore divided our report into the following sections:

1. Management of hypothyroidism: maternal and fetal aspects
2. Management of hyperthyroidism: maternal and fetal aspects
3. Gestational hyperemesis and hyperthyroidism
4. Autoimmune thyroid disease and miscarriage
5. Thyroid nodules and cancer
6. Iodine nutrition during pregnancy
7. Postpartum thyroiditis
8. Screening for thyroid dysfunction during pregnancy

The material herein is a condensed and abstracted version of the full report, which is published online at http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm. Each subsection provides recommendations followed by an abbreviated examination of evidence. Each recommendation is followed by a statement of strength of the recommendation and quality of the evidence. We have indicated the specific bibliographic citations on which each recommendation is based.

1.0. Management of hypothyroidism during pregnancy: maternal and fetal aspects

Recommendations

1.1. We recommend caution in the interpretation of serum free T_4 levels during pregnancy and that each laboratory establish trimester-specific reference ranges for pregnant women if using a free T_4 assay. The nonpregnant total T_4 range (5–12 μg/dl or 50–150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T_4 index ("adjusted T_4") appears to be a reliable assay during pregnancy. USPSTF recommendation level: B; evidence, fair (GRADE 2|⊕⊕◯◯) (1–3).

1.2.1. Overt maternal hypothyroidism is known to have serious adverse effects on the fetus (4–8). Therefore maternal hypothyroidism should be avoided. For overt hypothyroidism: USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯).

1.2.2. SCH (serum TSH concentration above the upper limit of the trimester-specific reference range with a normal free T_4) may be associated with an adverse outcome for both the mother and offspring. In retrospective studies, and in prospective studies on women with SCH and TPO-Ab+, T_4 treatment improved obstetrical outcome, but it has not been proved to modify long-term neurological development in the offspring. However, given that the potential benefits outweigh the potential risks, the panel recommends T_4 replacement in women with SCH. For obstetrical outcome: USPSTF recommendation level, C; evidence, fair (2|⊕⊕◯◯) (4–9); for neurological outcome: USPSTF recommendation level, I; evidence, poor (2|◯◯◯◯) (4–7, 9).

1.2.3. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯) (1, 10–12).

1.2.4. The T_4 dose usually needs to be incremented by 4 to 6 wk gestation and may require a 30% or more increase in dosage. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (12–15).

1.2.5. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. T_4 dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mIU/liter (in an assay using the International Standard) in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific TSH ranges. Thyroid function tests should be remeasured within 30–40 d and then every 4–6 wk. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (3, 11, 16, 17).

1.2.6. Women with thyroid autoimmunity who are euthyroid in the early stages of pregnancy are at risk of developing hypothyroidism and should be monitored for elevation of TSH above the normal range for pregnancy every 4–6 wk. USPSTF recommendation level: A; evidence, fair (1|⊕⊕⊕◯) (12, 14).

1.2.7. After delivery, most hypothyroid women need to decrease the T_4 dosage they received during pregnancy to the prepregnancy dose. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (18).

1.1.–1.2.7. Background and evidence

Overt hypothyroidism occurs in 0.3–0.5% of pregnancies, and SCH occurs in 2–3%. Thyroid autoantibodies are found in 5–15% of women during childbearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism, apart from iodine deficiency (19). Other causes include radioiodine ablation or surgery for hyperthyroidism, thyroid tumor surgery, congenital hypothyroidism, and rarely, lymphocytic hypophysitis.

Hypothyroid women are more likely to experience infertility, and they have an increased prevalence of abortion, anemia, gestational hypertension, placental abruption, and postpartum hemorrhage (4–9). Untreated maternal overt hypothyroidism is associated with adverse neonatal outcomes including premature birth, low birth

weight, and neonatal respiratory distress. There may be more fetal and perinatal death, and gestational hypertension may also contribute to the overall increase in neonatal risks. Women with gestational SCH were found in one study to have more preterm deliveries (20), and the offspring have more admissions to neonatal intensive care and an increased rate of respiratory distress syndrome (4). Even maternal TSH levels in the upper normal range are associated with increased fetal loss, as compared with lower "normal" levels (11).

Thyroid hormone contributes critically to normal fetal brain development (21). In moderate and severe iodine deficiency, there is significant childhood IQ reduction, preventable by gestational iodine supplementation. In iodine-sufficient areas, there is also a significantly increased risk of impairment in neuropsychological developmental indices, IQ scores, and school learning abilities in the offspring of hypothyroid mothers. A study in the United States showed that children born to untreated hypothyroid women had an IQ score seven points below the mean IQ of children born to healthy women (6). Children born to untreated hypothyroid mothers were three times more likely to have IQ that were 1 SD below the mean of controls. Early maternal low free T_4 has been associated with a lower developmental index in children at 10 months of age, and children born to mothers with prolonged low T_4 (until wk 24 or later) showed an 8- to 10-point deficit for motor and mental development (22). If free T_4 recovered spontaneously to normal later in gestation, infants had a normal development, suggesting that prolonged low T_4 was needed to impair fetal neural development. A recent study by Henrichs *et al.* (23) confirmed the adverse effects of maternal free T_4 levels in the lowest 10% of the normal range on early childhood cognitive development.

Diagnosis. Hypothyroidism may be suggested by cold sensitivity, fatigue, or dry skin or it may go unnoticed. Because many women remain asymptomatic, particular attention is required from obstetrical care providers for careful diagnosis and, if appropriate, thyroid function evaluation at the first prenatal clinic attendance. Only thyroid function tests confirm the diagnosis.

Total serum T_4 rises rapidly during the first trimester to roughly 150% of the nonpregnant range because of estrogen-induced elevation of T_4 binding globulin. Serum TSH elevation suggests primary hypothyroidism. Thyroid autoantibody titers [TPO-Ab or thyroglobulin (TG) antibodies] confirm an autoimmune origin (12). Serum TSH values are normally lowered, particularly near the end of the first trimester, because of the thyrotropic activity of elevated circulating human chorionic gonadotropin (hCG) concentrations. In the first trimester, the "normal" range is reduced to 0.1–2.5 mIU/liter (2, 24). Thus, a serum TSH within the classical reference range (0.4–4.0 mIU/liter) might be misdiagnosed as "normal" in women who have a slight TSH elevation, or hyperthyroidism may be wrongly suspected in normal women who have a blunted serum TSH.

Serum T_4 distinguishes between SCH and overt hypothyroidism, if normal, or clearly below normal for gestational age, respectively. Reference ranges provided by the manufacturers of most free T_4 measurement kits have been established using pools of nonpregnant normal sera, and such reference ranges are not valid during pregnancy. If free T_4 is the only test available, pregnancy-specific reference ranges should be established for each assay. The nonpregnant total T_4 range (5–12 μg/dl or 50–150 nmol/liter) can be adapted in the second and third trimesters by multiplying this range by 1.5-fold. Alternatively, the free T_4 index ("adjusted T_4") appears to be a reliable assay during pregnancy.

Treatment. Levothyroxine is the treatment of choice for maternal hypothyroidism, assuming adequate iodine nutrition (14). Hypothyroid pregnant women require larger levothyroxine doses than do nonpregnant patients. Women receiving T_4 antenatally usually should increase their dosage by 4–6 wk gestation to 30–50% above preconception dosage (14, 15). The increment is greater in women without residual functional thyroid tissue (*e.g.* radioiodine ablation, total thyroidectomy) than in those with residual thyroid tissue (*e.g.* Hashimoto's thyroiditis) (15). When serum TSH is first checked during pregnancy, the average increments of levothyroxine needed are 25–50 μg/d for serum TSH levels between 5 and 10 mIU/liter, 50–75 μg/d for serum TSH between 10 and 20 mIU/liter, and 75–100 μg/d for those with a serum TSH above 20 mIU/liter.

Management of a pregnant woman with normal TSH for pregnancy, but with thyroid hormone level by reliable assay below the pregnancy and trimester normal range on repeat assay, is controversial and requires further study (22, 23). However, in the opinion of the committee, partial replacement therapy may be initiated at the discretion of the caregiver, with continued monitoring.

2.0. Management of hyperthyroidism: maternal and fetal aspects

Recommendations

2.1. Management of maternal hyperthyroidism: maternal aspects

2.1.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy

and gestational thyrotoxicosis because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by the presence of clinical evidence of autoimmune thyroid disease, a typical goiter, and the presence of TRAb. TPO-Ab may be present in either case. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯) (24–26).

2.1.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, ATD therapy should be either initiated (before pregnancy if possible, and for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T_4 at the upper limit of the nonpregnant reference range. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯); or to maintain total T_4 at 1.5 times the upper limit of the normal reference range, or the free T_4 index in the upper limit of the normal reference range. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯) (27).

2.1.3. PTU, if available, is recommended as the first-line drug for treatment of hyperthyroidism during the first trimester of pregnancy, because of the possible association of MMI with specific congenital abnormalities that occur during first trimester organogenesis. MMI may also be prescribed if PTU is not available or if a patient cannot tolerate or has an adverse response to PTU. MMI 10 mg is considered to be approximately equal to 100–150 mg of PTU. Recent analyses reported by the FDA indicate that PTU may rarely be associated with severe liver toxicity. For this reason, we recommend that clinicians change treatment of patients from PTU to MMI after the completion of the first trimester. Available data indicate that MMI and PTU are equally efficacious in the treatment of pregnant women. Practitioners should use their clinical judgment in choosing the ATD therapy, including the potential difficulties involved in switching patients from one drug to another. If switching from PTU to MMI, thyroid function should be assessed after 2 wk and then at 2- to 4-wk intervals. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯). Although liver toxicity may appear abruptly, it is reasonable to monitor liver function in pregnant women on PTU every 3–4 wk and to encourage patients to promptly report any new symptoms. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯) (28–34).

2.1.4. Subtotal thyroidectomy may be indicated during pregnancy as therapy for maternal Graves' disease if: 1) a patient has a severe adverse reaction to ATD therapy; 2) persistently high doses of ATD are required (over 30 mg/d of MMI or 450 mg/d of PTU); or 3) a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯) (35–37).

2.1.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯) (27, 38).

2.2. Management of maternal hyperthyroidism: fetal aspects

2.2.1. Because thyroid receptor antibodies (thyroid receptor stimulating, binding, or inhibiting antibodies) freely cross the placenta and can stimulate the fetal thyroid, these antibodies should be measured by 22 wk gestational age in mothers with: 1) current Graves' disease; or 2) a history of Graves' disease and treatment with ^{131}I or thyroidectomy before pregnancy; or 3) a previous neonate with Graves' disease; or 4) previously elevated TRAb. Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯) (39–42).

2.2.2. ^{131}I should not be given to a woman who is or may be pregnant. If inadvertently treated, the patient should be promptly informed of the radiation danger to the fetus, including thyroid destruction if treated after the 12th week of gestation. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯). There are no data for or against recommending termination of pregnancy after ^{131}I exposure. USPSTF recommendation level: I; evidence, poor (2⊕◯◯◯) (43–47).

2.2.3. In women with TRAb or thyroid-stimulating Ig elevated at least 2- to 3-fold the normal level, and in women treated with ATD, maternal free T_4 and fetal thyroid dysfunction should be screened for during the fetal anatomy ultrasound (18th-22nd wk) and repeated every 4–6 wk or as clinically indicated. Evidence of fetal thyroid dysfunction could include thyroid enlargement, growth restriction, hydrops, presence of goiter, advanced bone age, tachycardia, or cardiac failure. If fetal hyperthyroidism is diagnosed and thought to endanger the pregnancy, treatment using MMI or PTU should be given with frequent clinical, laboratory, and ultrasound monitoring. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯) (39, 41, 48–50).

2.2.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical and sonographic data, and the information gained would change the treatment. USPSTF recommendation level: B; evidence, fair (2|⊕◯◯◯) (41, 51–56).

2.2.5. All newborns of mothers with Graves' disease (except those with negative TRAb and not requiring ATD)

should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯) (40, 48, 52).

2.1.1–2.2.5. Background and evidence

The prevalence of hyperthyroidism in pregnancy ranges from 0.1 to 0.4%, with Graves' disease accounting for 85% of cases (28, 57, 58). The activity level of Graves' disease may fluctuate during gestation, with exacerbation during the first trimester and improvement by late gestation. Hyperthyroidism of Graves' disease may be aggravated by high levels of hCG in the first trimester.

Because nonspecific symptoms of hyperthyroidism may be mimicked by normal pregnancy, the presence of a goiter, especially with a bruit or thrill, may point to a diagnosis of true Graves' disease. Thyroid function tests must be interpreted in the context of the normal gestational changes of decreased serum TSH and increased T_4 and T_3 levels.

Patients suspected of having hyperthyroidism require measurement of serum TSH, T_4 or free T_4, T_3 levels, and TRAb. However, interpretation of thyroid function tests must be made in relation to the hCG-mediated decrease in serum TSH levels and the increase in T_4 binding globulin concentrations that occur during pregnancy (59–61). In the normal pregnant woman, TSH levels typically are suppressed in the mid to late first trimester.

Fetal hyperthyroidism due to the transplacental passage of maternal TSH receptor stimulating antibody (TRAb) levels is rare (0.01% of pregnancies), but it should be considered in any woman with a past or current history of Graves' disease and may require treatment with maternal antithyroid medications.

Maternal hyperthyroidism is associated with both gestational and fetal risks that are related to the disease itself and/or to the medical treatment of the disease. Inadequately treated maternal thyrotoxicosis is associated with an increased risk of medically indicated preterm delivery, intrauterine growth restriction and low birth weight, preeclampsia, congestive heart failure, and fetal death (62). In addition, overtreatment of the mother with thioamides can result in iatrogenic fetal hypothyroidism (51), but undertreatment of maternal hyperthyroidism may lead to central congenital hypothyroidism (63, 64).

Fetal hyperthyroidism can be associated with intrauterine growth restriction, fetal tachycardia, fetal goiter, advanced bone age, fetal hydrops, preterm delivery, and fetal death (40–42, 53, 56, 65). The diagnosis is suggested by any of these signs or abnormalities. Maternal TRAb levels able to induce fetal hyperthyroidism are usually over three times the upper normal limit.

PTU and MMI or its derivative carbimazole are the mainstays of treatment. Recently, the Adverse Event Reporting System of the FDA has focused attention on the relation between hepatotoxicity and PTU (29). This finding has led to a recommendation that PTU use in pregnancy be limited to the first trimester, and then treatment be switched to MMI. Use of MMI during the first trimester has been associated with a possible embryopathy.

3.0 Gestational hyperemesis and hyperthyroidism

Recommendations

3.1. Thyroid function tests (TSH, total T_4, or free T_4 index, or free T_4) and TRAb should be measured in patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria) and clinical features of hyperthyroidism. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯) (24, 27, 66–68).

3.2. Most women with hyperemesis gravidarum, clinical hyperthyroidism, suppressed TSH, and elevated free T_4 do not require ATD treatment. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Clinical judgment should be followed in women who appear significantly thyrotoxic or who have in addition serum total T_3 values above the reference range for pregnancy. Beta blockers such as metoprolol may be helpful and may be used with obstetrical agreement. USPSTF recommendation level: B; evidence, poor (2|⊕◯◯◯) (13, 25, 26, 66–68).

3.3. Women with hyperemesis gravidarum and diagnosed to have Graves' hyperthyroidism (free T_4 above the reference range or total $T_4 > 150\%$ of top normal pregnancy value, TSH < 0.01 mIU/liter, and presence of TRAb) will require ATD treatment, as clinically necessary. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕) (13, 25, 26, 66–68).

3.1–3.3 Background and evidence

Gestational hyperthyroidism (GH), also referred as gestational thyrotoxicosis or gestational transient thyrotoxicosis, is defined as transient hyperthyroidism, limited to the first half of pregnancy, characterized by elevated serum free T_4 and suppressed or undetectable serum TSH, in the absence of thyroid autoimmunity. GH is typically associated with hyperemesis gravidarum, defined as severe vomiting in early pregnancy that causes more than 5% weight loss, dehydration, and ketonuria and occurs in 0.5–10 cases per 1000 pregnancies. The etiology of thyroid stimulation is thought to be hCG itself, or molecular variant proteins related to hCG. Multiple gestation is another recognized cause of GH. Very high elevations of hCG occurring in patients with hydatidiform mole or choriocarcinoma are often associated with clinical hyperthyroidism. *TSHR* mutations with functional hypersensitivity to hCG have also been recognized as a rare cause of severe GH. Other isolated rare cases of GH, such as hy-

perplacentosis and hyperreactio luteinalis, have been reported. The condition can cause severe morbidity and may require frequent visits to the emergency room or admission to the hospital for management of dehydration, electrolyte abnormalities, psychological support, and occasionally parenteral nutrition (25, 26).

In women with GH, the serum TSH is suppressed or undetectable; serum total T_4 and free T_4 are elevated, but the free T_3 is elevated less frequently. Women with hyperemesis and elevated thyroid hormone levels most commonly do not have other clinical evidence of Graves' disease and lack the TSH receptor antibodies typically present in Graves' disease. A small portion of these patients have clinical hyperthyroidism. Clinical symptoms of hyperthyroidism antedating pregnancy, the presence of goiter, ophthalmopathy, and laboratory evidence of autoimmunity favor the diagnosis of Graves' hyperthyroidism. Because many common signs and symptoms of hyperthyroidism may be mimicked by normal pregnancy, the clinical challenge is to differentiate these disorders (13, 25, 26, 66–68). There is disagreement as to whether thyroid hormone should be measured in all pregnancies with hyperemesis, or only when clinical features of hyperthyroidism are present. Some authorities suggest that measurement of thyroid function tests may safely be limited to those women with clinical evidence suggestive of hyperthyroidism.

There is no clear evidence in the medical literature that patients diagnosed with GH have benefited from antithyroid therapy, but only a few patients have been reported who received ATD for a few weeks. The available data indicate that most women with hyperemesis, with no or mild clinical evidence of hyperthyroidism, suppressed TSH, and elevated free T_4, remit spontaneously. No clear data are available to support the use of ATD in the management of women with GH, but clinical judgment should be followed in women with clear signs of hyperthyroidism and elevated free T_4 and free T_3, or total T_3 above the normal pregnancy range (13, 25, 26, 66–68).

4.0. Autoimmune thyroid disease and miscarriage

Recommendations

4.1. A positive association exists between the presence of thyroid antibodies and pregnancy loss. Universal screening for antithyroid antibodies, and possible treatment, cannot be recommended at this time. As of January 2011, only one randomized interventional trial has suggested a decrease in the first trimester miscarriage rate in euthyroid antibody-positive women, but treatment duration was very brief before the outcome of interest. However, because women with elevated anti-TPO antibodies are at increased risk for progression of hypothyroidism, if identified such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (2⌁⊕◯◯◯) (69–72).

4.1. Background and evidence

A 2- to 5-fold increased risk of miscarriage has been found in unselected populations of euthyroid women with autoimmune thyroid disease (70). Most but not all studies have also demonstrated an association between thyroid antibodies and recurrent miscarriage in euthyroid patients (69, 71). However, the data are imperfect because the timing of sample collection for thyroid antibody measurement was not always specified, the prevalence of thyroid antibodies varied widely, and studies measured TPO-Ab or TGAb or both. In some of these reports, thyroid antibodies may simply serve as a marker for generalized autoimmune disease. TSH levels have been found slightly but significantly higher (within the normal range) in euthyroid women with thyroid autoimmunity than in those women without it. In some of these studies, women with thyroid antibodies were older than those without antibodies.

The data are less clear on the miscarriage rate in infertile patients undergoing assisted reproductive technology, according to the presence or absence of thyroid antibodies. Half of the studies find that the presence of thyroid antibodies is associated with a 2-fold increased risk for spontaneous miscarriage in euthyroid women undergoing *in vitro* fertilization (73, 74). No significant difference was found in the other studies, but in some a trend toward a higher miscarriage rate was noticed in the thyroid antibody-positive women. The largest series, although retrospective, failed to demonstrate an adverse effect on miscarriage rates in antibody-positive *vs.* antibody-negative women undergoing assisted reproductive technology (73). It is not possible to draw a definitive conclusion based on available data.

Treatment

Negro *et al.* (72) performed a prospective, randomized trial of 984 unselected women who were screened for TPO antibody positivity and thyroid function tests on their first obstetrical visit. The 115 women who were TPO-Ab+ were divided into two groups: group A (n = 57) included TPO-Ab+ women treated with levothyroxine; group B (n = 58) included TPO-Ab+ women who received no levothyroxine intervention. Group C (n = 869) consisted of all TPO-Ab− women, none of whom received levothyroxine. The first trimester miscarriage rate was significantly lower in groups A (3.5%) and C (2.4%) than in group B (13.8%) ($P < 0.05$). However, the mean gestational age at the time of miscarriage was 8.5 wk, and treatment on average did not start until 10.5 wk gestation

(40% on treatment by 8 wk and 79% by 12 wk). It should also be taken into account that TSH levels during pregnancy were significantly higher, whereas free T_4 levels were significantly lower (although in the normal range) in group B than in group C.

In a retrospective study in Belgium, 42 TPO-Ab+ patients received levothyroxine treatment during pregnancy, and their evolution was compared with 709 TPO-Ab− women. No significant differences in the obstetrical complications rate were observed between the groups, but early miscarriages were not investigated in this study. A further limitation to this study is that a TPO-Ab+ group without levothyroxine treatment was not included (75).

Regarding medical intervention in thyroid antibody-positive women with recurrent abortion, the studies reviewed demonstrate that T_4 or iv Ig treatments may decrease the miscarriage rate (64–74, 75, 78). However, many of these women had evidence of other autoimmunity, and limitations in the design of each study preclude any conclusion regarding the efficacy of medical intervention.

A single study has evaluated the impact of T_4 therapy in euthyroid antibody-positive infertile women who underwent assisted reproduction techniques (73). Although the miscarriage rate was lower in women who received T_4 (33%) than in those who did not (52%), this difference failed to reach statistical significance (a failing that may have been secondary to the small sample size).

Women with recurrent pregnancy loss are reported to have lower selenium levels in hair and in red blood cells (77). Selenium substitution and treatment with selenomethionine may decrease TPO-Ab levels in euthyroid subjects (78). Large randomized studies are needed to assess the contribution of selenium in the etiology of recurrent pregnancy loss and the potential benefits of its supplementation.

Besides the risk of miscarriages, thyroid autoimmunity may be correlated with a higher frequency of preterm deliveries (between 2- and 3-fold higher than in pregnancy without thyroid antibodies) and low birth weight. According to a study by Negro *et al.* (72) in Italy, the preterm delivery rate was higher (22.4%) in TPO-Ab+ women without treatment than in TPO-Ab+ women on levothyroxine treatment (7%) or in TPO-Ab− women (8.2%) ($P < 0.05$), although the gestational age at delivery was not specified between the groups.

Recently, 9247 singleton pregnancies were prospectively studied in Finland. Perinatal mortality was 2- to 3-fold greater in women who were TPO-Ab+ or TG antibody positive in the first trimester as compared with those who were antibody negative, but most of these infants were also born preterm (79).

Intellectual and motor development score evaluations were performed at 25–30 months of age on the children from 34 euthyroid mothers with elevated titers of TPO-Ab at 16–20 wk gestation. The mean intelligence score was 10 points lower and the mean motor score 9 points lower than those of the controls ($P = 0.001$ and $P < 0.001$, respectively) (80). More studies are necessary to confirm whether thyroid autoimmunity could be considered a risk factor for impaired neurodevelopment, independent of the thyroid function.

5.0 Thyroid nodules and cancer

Recommendations

5.1. FNA cytology should be performed for predominantly solid thyroid nodules greater than 1 cm discovered in pregnancy. Women with nodules 5 mm to 1 cm in size should be considered for FNA if they have a high-risk history or suspicious findings on ultrasound, and women with complex nodules 1.5–2 cm or larger should also receive an FNA. During the last weeks of pregnancy, FNA can reasonably be delayed until after delivery. Ultrasound-guided FNA is likely to have an advantage for maximizing adequate sampling. USPSTF recommendation level: B; evidence, fair (1|⊕⊕⊕◯) (81–84).

5.2. When nodules discovered in the first or early second trimester are found to be malignant or highly suspicious on cytopathological analysis, to exhibit rapid growth, or to be accompanied by pathological neck adenopathy, pregnancy need not be interrupted, but surgery should be offered in the second trimester. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease and who prefer to wait until the postpartum period for definitive surgery may be reassured that most well-differentiated thyroid cancers are slow growing and that delaying surgical treatment until soon after delivery is unlikely to change disease-specific survival. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯) (75, 83–85).

5.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women with a previously treated thyroid cancer, in those with an FNA positive for or suspicious for cancer, or in those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more than low risk patients from a greater degree of TSH suppression. The free T_4 or total T_4 levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level: I; evidence, poor (⊕◯◯◯) (86).

5.4. RAI with ^{131}I should not be given to women who are breastfeeding or for at least 4 wk after nursing has ceased. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕). Furthermore, pregnancy should be

avoided for 6 months to 1 yr in women with thyroid cancer who receive therapeutic RAI doses to ensure stability of thyroid function and confirm remission of thyroid cancer. USPSTF recommendation level: B; evidence, fair (1I⊕⊕◯◯) (87–89).

5.1.–5.4 Background and evidence

There is biological plausibility that pregnancy could promote the onset of growth of a benign or malignant nodule due to a pregnancy-induced relative iodine deficiency, the thyroid-stimulating effect of hCG, and high estrogen levels. Only data from areas of mild iodine insufficiency are available and suggest that nodules may be more prevalent in pregnant women and that the volume may increase in gestation (82). Several retrospective studies reported a malignancy rate of about 15%, with one exceptional study finding of 50% (90), and these limited data suggest that the malignancy rate is either similar to or possibly greater than that seen in the general population.

The diagnostic evaluation of a single thyroid nodule or a nodule found in a multinodular goiter discovered during pregnancy should be similar to that of nonpregnant patients (75, 91) and relies primarily on the results of thyroid ultrasound and FNA biopsy. Nodules suspected to be hyperfunctioning may await further assessment with a radionuclide scan until postpartum. For the rare nodule causing severe hyperthyroidism, ATD treatment and operation may be advisable. Evaluating the nodule during pregnancy is often helpful to the mother in making decisions regarding breastfeeding and the potential need for postpartum adjunctive therapy with radioiodine after surgical removal of a cancer.

There is no clear evidence that pregnancy worsens the survival from well-differentiated thyroid cancer found during an existing pregnancy (75, 92). However, if the result of FNA is consistent with or highly suggestive of papillary, follicular, anaplastic, or medullary carcinoma, or has suspicious sonographic characteristics, surgery should be offered in the second trimester. During the first trimester, there is concern over the possible teratogenic effects on the fetus, and surgery of any type is associated with increased early fetal loss (93). Surgery in the third trimester is associated with a higher incidence of preterm labor. Fetal loss or significant complications are rare in the second trimester (93). There is some evidence that thyroid cancers discovered during pregnancy have a greater chance of recurrence when defined by increasing serum markers of TG or TG antibodies (94). However, operation for papillary cancer may be postponed with little increased risk until after delivery if the patient is hesitant to undergo surgery during pregnancy (75, 91–93), and there are no data that surgery undergone during pregnancy as compared with immediately postpartum affects survival.

If a nodule suspicious of cancer is discovered in the third trimester, further workup and treatment can be delayed until after delivery unless the nodule is rapidly growing or associated with a poor prognosis. Exogenously administered thyroid hormone is recommended for suspicious or malignant nodules to achieve a suppressed TSH with a free T_4 or total T_4 in the upper normal range for pregnancy to avoid both maternal and fetal complications.

Several series have examined the natural history of cancer recurrence in women who became pregnant after receiving successful treatment for thyroid cancer, and in all studies there was no evidence that thyroid cancer was adversely influenced by the pregnancy (95). Monitoring with TG is recommended for women who have received RAI, and women may be maintained on suppressive doses of T_4 that do not cause overt hyperthyroidism.

Multiple studies have indicated that prior treatment with ^{131}I does not appear to affect subsequent pregnancy outcomes including infertility, congenital malformations, miscarriages, stillbirths, prematurity, low birth weight, infant mortality, the rate of nonthyroidal malignancy in the offspring, or intellectual development (96). However, nursing women should not be offered ^{131}I therapy because of the concentration of isotope in the lactating breast and transfer of the isotope to the infant. Conception should be avoided for at least 1 yr after ^{131}I ablative treatment to confirm remission of thyroid cancer and stability of thyroid function tests (87).

6.0. Iodine nutrition during pregnancy

Recommendations

6.1. Women in the childbearing age should have an average iodine intake of 150 μg/d. As long as possible before pregnancy and during pregnancy and breastfeeding, women should increase their daily iodine intake to 250 μg on average. USPSTF recommendation level: A; evidence, good (1I⊕⊕⊕◯) (59, 97–99).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily RNI for iodine, *i.e.* 500 μg iodine per day. USPSTF recommendation level: I; evidence, poor (2I⊕◯◯◯) (59, 97–99).

6.3. Although not advised as a part of normal clinical practice, the adequacy of the iodine intake during pregnancy can be assessed by measuring UIC in a representative cohort of the population. UIC should ideally range between 150 and 250 μg/liter. If there is significant concern, the caregiver should assay TSH and thyroid hormone levels. USPSTF recommendation level: A; evidence, good (1I⊕⊕⊕⊕).

6.4. To reach the daily recommended nutrient intake for iodine, multiple means must be considered, tailored

to the iodine intake level in a given population. Different situations must therefore be distinguished: 1) countries with iodine sufficiency and/or with a well-established USI program; 2) countries without a USI program or with an established USI program where the coverage is known to be only partial; and 3) remote areas with no accessible USI program and difficult socioeconomic conditions. USPSTF recommendation level: A; evidence, good (1⊕⊕⊕⊕) (100–104).

6.5. We recommend that once-daily prenatal vitamins should contain 150–200 μg iodine and that this be in the form of potassium iodide or iodate, the content of which is verified to ensure that all pregnant women taking prenatal vitamins are protected from iodine deficiency. Ideally, supplementation should be started before conception. Preparations containing iron supplements should be separated from thyroid hormone administration by at least 4 h. USPSTF recommendation level: B; evidence, fair (2⊕⊕◯◯) (105).

6.6 We recommend that breastfeeding women maintain a daily intake of 250 μg of iodine to ensure that breast milk provides 100 μg iodine per day to the infant. USPSTF recommendation level: A; evidence, good (1⊕⊕⊕◯).

6.1.–6.6. Background and evidence

Iodine is essential for the synthesis of T_4, a critical hormone for fetal brain development. Maternal T_4 is the only source of hormone before the development of the fetal thyroid at 13–15 wk gestation; maternal iodine is still required for fetal thyroid hormone synthesis thereafter. During pregnancy, thyroid hormone synthesis increases by 20–40%, compensating for estrogen-induced T_4 binding globulin and increased iodine clearance. Therefore, maternal iodine intake must be increased during pregnancy. Iodine stores should be replete at conception with an iodine intake of more than 150 μg/d (97).

Worldwide, iodine deficiency is the leading cause of preventable fetal brain damage (98, 106). Severe iodine deficiency causes endemic goiter, hypothyroidism, cretinism, decreased fertility, miscarriage, increased infant mortality, trophoblastic or embryonic fetal disorders, and mental retardation (99). Even mild to moderate iodine deficiency during pregnancy can lead to increased TSH levels and may cause both maternal and fetal goiter (98). Mild maternal subclinical or overt hypothyroidism due to iodide deficiency may result in intellectual deficit and/or neuropsychomotor deficits in offspring. These problems may be prevented if iodine supplementation is started in early pregnancy (100).

Breastfed infants are dependent upon maternal iodine intake. The mammary gland concentrates iodine, and breast milk supplies 100 μg/d to the infant. Mothers should continue to have an intake of 250 μg iodide per day during lactation. A World Health Organization expert panel (97) recommended iodine intake of 200–300 μg/d in pregnant and breastfeeding women, based on population studies, noting prevention of maternal hypothyroidism and goiter and fetal goiter.

Environmental iodine varies widely geographically, as does iodine supplementation of food, salt, or oil. The best parameter to evaluate the adequacy of iodine nutrition in a population is urinary iodine excretion (UIE). During pregnancy, the UIE should be 150–250 μg/d (97, 100). Although UIE is useful for health population studies, it is not a valid diagnostic criterion in individuals.

The prevalence of iodine deficiency (UIE $<$ 100 μg/d) ranges from 11% in North and South America to 42% in some parts of Africa, and as high as 50% in some parts of Europe and China (107). Recent surveys of iodine nutrition in pregnant women are limited, and a global estimate of the prevalence of iodine deficiency in pregnancy is not possible (105). More recent surveys of urinary iodine in limited geographical areas continue to reveal significant numbers of women with suboptimal iodine nutrition, defined as urinary iodine less than 150 μg/liter during pregnancy, even in areas where iodization of salt has been implemented (97, 105).

In the United States, overall urinary iodine declined substantially from the 1970s to the 1990s, but stabilized at 168 μg/liter in 2002 and 160 μg/liter in 2002–2004. Concomitantly, the mean urinary iodine in pregnant women in the United States decreased from 327 μg/liter to 140 μg/liter from 1971–1974 to 1988–1994, with an increase in the prevalence of moderately low urine iodine concentrations ($<$50 μg/liter) from 0.6 to 1.9% (108). The most recent National Health and Nutrition Examination Survey data for pregnant women in the United States note stability of median urinary iodine in pregnancy from 141 μg/liter (1988–1994), 173 μg/liter (2001–2002), and 181 μg/liter (2003–2004), but with a substantial number of women still having low urine iodine (21% $<$ 100 μg/liter and 4.7% $<$ 50 μg/liter) at the most recent report (97, 108, 109).

In an individual pregnant woman, the best surrogate to determine iodine sufficiency is maternal thyroid function. Iodine restriction during pregnancy results in reduction of free T_4 and increases in TSH, TG, T_3/T_4 ratio, and thyroid volume, with goiter formation in both the mother and fetus. However, Hollowell and Haddow (99) found no evidence of low T_4 or high ($>$4.5 mIU/liter) TSH values in a small sample of U.S. pregnant women with urinary iodine less than 50 μg/liter.

The recommended method for correcting iodine deficiency worldwide is USI, but in some countries where USI

cannot be implemented, massive annual doses of slow-release iodinated oil are given to children and to women in the reproductive age group. Four hundred milligrams of oral iodine will cover the thyroidal needs for an adult for about a 1-yr period (99).

Fortification should begin as soon as possible in a pregnant woman, ideally no later than the first trimester to allow rapid adaptation to the increased needs of pregnancy. It is important to note that even in a population judged to be iodine sufficient, individual women may have inadequate iodine intake before and during pregnancy, thus emphasizing the need for routine supplementation of all pregnant women with adequate iodine in the form of prenatal vitamins. Women should be counseled to take prenatal supplements containing the RNI for pregnancy and to ascertain that their vitamin preparations in fact do contain adequate amounts of iodine. Supplementation should begin as soon as pregnancy is confirmed.

Excess iodine intake may, paradoxically, lead to an increase in hypothyroidism in subjects at risk for autoimmune thyroid disease and to hyperthyroidism, particularly when iodine is newly introduced in populations with previous iodine deficiency and multinodular goiters. Excess iodine is empirically defined as double the RNI (110).

7.0. Postpartum thyroiditis

Recommendations

7.1. There are insufficient data to recommend screening of all women for PPT. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯) (111, 112).

7.2. Women known to be TPO-Ab+ should have TSH measured at 6–12 wk gestation and at 6 months postpartum, or as clinically indicated. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯) (112–116).

7.3. Because the prevalence of PPT in women with type 1 diabetes, Graves' disease in remission, and chronic viral hepatitis is greater than in the general population, screening by TSH is recommended at 3 and 6 months postpartum. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯).

7.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period after the episode of PPT. An annual TSH level should be performed in these women. USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕◯) (113, 117–119).

7.5. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 mIU/liter and who are not planning a subsequent pregnancy do not necessarily require intervention, but should, if untreated, be remonitored in 4–8 wk. When a TSH above the reference range continues, women should be treated with levothyroxine. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯) (112).

7.6. There is insufficient evidence to conclude whether an association exists between PPD and either PPT or thyroid antibody positivity (in women who did not develop PPT). USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯). However, because hypothyroidism is a potentially reversible cause of depression, women with PPD should be screened for hypothyroidism and appropriately treated. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯) (120–126).

7.1.–7.6. Background and evidence

PPT is the occurrence of thyrotoxicosis, hypothyroidism, or thyrotoxicosis followed by hypothyroidism in the first year postpartum in women who were without clinically evident thyroid disease before pregnancy. It is believed to be caused by an autoimmunity-induced discharge of preformed hormone from the thyroid. PPT occurs almost exclusively in women who are thyroid antibody positive.

Prevalence in unselected populations. The reported prevalence of PPT varies globally, and the mean prevalence in prospective studies in iodine-sufficient areas in which at least two thirds of the cohort was followed for at least 5 months postpartum is approximately 7% (127). Incidence is affected by genetic influences and iodine intake.

Prevalence in women with type 1 diabetes mellitus (DM). The prevalence of TPO antibodies in patients with type 1 DM reported in the Familial Autoimmune and Diabetes Study was 26.6%. In accord with this, the incidence of PPT in women with type 1 DM is higher than in an unselected population, with a range of 18–25% (114).

Predictors of PPT. PPT is caused by the immunological perturbations that occur during pregnancy and postpartum. Some of the immunological abnormalities are observed before the onset of thyroid dysfunction (128). Among these, TPO-Ab positivity is the most useful marker for the prediction of postpartum thyroid dysfunction (129). From 40–60% of women with positive TPO-Ab in early pregnancy develop postpartum thyroid dysfunction (112, 123). The majority of mothers with high titers of antibody develop postpartum thyroid dysfunction (129).

Thyrotoxic symptoms of women with PPT. The thyrotoxic phase of PPT occurs between 1 and 6 months postpartum (most commonly at 3 months) and usually lasts only 1–2 months. It is important to differentiate between the thy-

rotoxic phase of PPT and Graves' disease presenting *de novo* in the postpartum period. Symptoms during the thyrotoxic phase of PPT tend to be milder than during hyperthyroidism due to Graves' disease. Furthermore, 95% of women with Graves' disease are TSH receptor antibody positive. In contrast to Graves' disease, PPT is characterized by decreased RAI uptake (measurement of ^{131}I uptake is contraindicated in lactating women). From 20–30% of patients who develop PPT have only thyrotoxic symptoms. Fatigue, palpitations, weight loss, heat intolerance, nervousness, anxiety, and irritability are more prevalent in women with PPT than in euthyroid women (129). The frequency of asymptomatic hyperthyroidism among patients with PPT is approximately 30% (112).

Hypothyroid symptoms of women with PPT. The hypothyroid phase of PPT usually occurs between 3 and 8 months (most commonly at 6 months). Approximately 40–45% of women who develop only the hypothyroid phase of PPT will experience symptoms, whereas 25–35% of women who develop hypothyroidism after the hyperthyroid phase will experience hypothyroid symptoms (130). Hypothyroidism tends to happen earlier when preceded by thyrotoxicosis than when it occurs alone. The hypothyroid phase usually lasts 4–6 months. In systematic studies, fatigue, loss of concentration, poor memory, constipation, and possibly depression were most frequently experienced (128, 129).

Association of PPT with PPD. The incidence of PPD in nonselected populations using Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revision (DSMIII-R) criteria appears to be approximately 10% (120). Several studies have addressed whether there is an association between PPD and positive thyroid antibody status alone, in addition to the possible association between PPD and women who have PPT with thyroid dysfunction. At present, reported studies have not revealed a consistent association between PPD and either PPT or the presence of thyroid antibody positivity in euthyroid women postpartum.

Optimal treatment for PPT. There have been no controlled studies evaluating the optimal treatment for PPT. In the thyrotoxic phase of PPT, intervention with propranolol was recommended for women with symptoms of palpitations, fatigue, heat intolerance, and/or nervousness. Treatment decisions for women in the hypothyroid phase of PPT depend on both the degree of hypothyroidism and whether the woman is attempting pregnancy. Asymptomatic women who are not planning a subsequent pregnancy and whose TSH level is between 4 and 10 mIU/liter do not necessarily require intervention and should, if untreated, be reevaluated in 4–8 wk. When a TSH above the reference range continues postpartum, women should be treated with levothyroxine. Women with a TSH between 4 and 10 mIU/liter who are either symptomatic or attempting to become pregnant should be treated with T_4.

Follow-up for women with PPT. Postpartum thyroid dysfunction is typically transient in nature, with the majority of women returning to euthyroidism by the end of the first postpartum year. However, even after recovery from hypothyroidism, abnormalities in ultrasonography and/or iodide perchlorate discharge tests persist, reflecting underlying chronic autoimmune thyroiditis. It is therefore not surprising that a small percentage of women never recover from the initial hypothyroid phase, and 20–64% of women develop permanent hypothyroidism during long-term follow-up (117, 119).

8.0. Screening for thyroid dysfunction during pregnancy

Recommendations

8.1a. Universal screening of healthy women for thyroid dysfunction *before* pregnancy is not recommended. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯).

8.1b. However, caregivers should identify individuals at "high risk" for thyroid illness (Table 1) on the basis of their medical history, physical exam, or prior biochemical data. When such individuals are identified, prenatal measurement of serum TSH is recommended. If it is above 2.5 mIU/liter, the test should be confirmed by repeat assay. Although no randomized controlled trials are available to guide a response, the committee believes it is appropriate to give low-dose T_4 treatment to bring TSH below 2.5 mIU/liter. This treatment can be discontinued if the woman does not become pregnant or postpartum. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯) (22, 131–133).

TABLE 1. Recommended patient profiles for targeted thyroid disease case finding in women seeking pregnancy or newly pregnant

Women over age 30 yr
Women with a family history or autoimmune thyroid disease or hypothyroidism
Women with a goiter
Women with thyroid antibodies, primarily thyroid peroxidase antibodies
Women with symptoms or clinical signs suggestive of thyroid hypofunction
Women with type 1 DM or other autoimmune disorders
Women with infertility
Women with a prior history of miscarriage or preterm delivery
Women with prior therapeutic head or neck irradiation or prior thyroid surgery
Women currently receiving levothyroxine replacement
Women living in a region with presumed iodine deficiency

8.2a. All women considering pregnancy with known thyroid dysfunction and receiving levothyroxine should be tested for abnormal TSH concentrations *before* pregnancy. USPSTF recommendation level: B; evidence, fair (1|⊕⊕◯◯) (134, 135).

8.2b. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach before pregnancy a TSH level not higher than 2.5 mIU/liter. USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯) (132–134, 136).

8.2c. All women receiving levothyroxine should be verbally screened prenatally to assess their understanding of changing levothyroxine requirements after conception. These women should be counseled to contact a physician or medical professional immediately upon a missed menstrual cycle or suspicion of pregnancy to check their serum TSH level. An additional recommendation may be to increase their levothyroxine dose by 30%, which is often two additional tablets per week (nine tablets per week instead of seven tablets), until their serum TSH can be checked. USPSTF recommendation level: B; evidence, fair (2|⊕⊕◯◯) (12–14, 135).

8.3a. Universal screening for the presence of anti-TPO antibodies either before or during pregnancy is not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕◯◯◯).

8.3b. However, women with elevated anti-TPO antibodies are at increased risk for miscarriage, preterm delivery, progression of hypothyroidism, and PPT. Therefore, if identified, such women should be screened for serum TSH abnormalities before pregnancy, as well as during the first and second trimesters of pregnancy. USPSTF recommendation level: C; evidence, fair (1|⊕⊕◯◯) (72, 132) (see also Section 8.5).

8.4a. The committee could not reach agreement with regard to screening recommendations for all *newly pregnant* women. Two versions are therefore presented.

8.4a1. Some members recommended screening of all pregnant women for serum TSH abnormalities by the ninth week or at the time of their first visit. USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯) (6, 9, 22, 72, 137) (Authors supporting: L.D.G., J.R., J.H.L., N.A., C.J.E.).

8.4a2. Some members recommended neither for nor against universal screening of all pregnant women for TSH abnormalities at the time of their first visit. These members strongly support aggressive case finding to identify and test high-risk women (Table 1) for elevated TSH concentrations by the ninth week or at the time of their first visit before or during pregnancy, and they recognize that in some situations ascertainment of the individual's risk status may not be feasible. In such cases, and where the local practice environment is appropriate, testing of all women by wk 9 of pregnancy or at the first prenatal visit is reasonable. USPSTF recommendation level: I; evidence, poor (2|⊕◯◯◯) (72, 80, 137, 138) (Authors supporting: M.A., E.K.A., J.M., L.B., S.S., S.J.M., D.L., R.H.C.).

8.4b. If serum TSH is greater than 2.5 mIU/liter at the time of testing (or >3.0 mIU/liter in the second trimester), levothyroxine therapy should be instituted. For overt hypothyroidism, USPSTF recommendation level: A; evidence, good (1|⊕⊕⊕⊕); for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯); and for SCH and obstetrical outcome, USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯) (4, 5, 9, 131, 137).

8.4c. If TSH concentration is 2.5–10 mIU/liter, a starting levothyroxine dose of 50 μg/d or more is recommended. Other thyroid preparations (such as T_3) are not recommended. USPSTF recommendation level: C; evidence, fair (2|⊕⊕◯◯) (135).

8.5. Women at high risk for PPT in the postpartum months should be screened via assessment of serum TSH. These high-risk groups include: 1) women known to be TPO Ab+; 2) women with type 1 diabetes; and 3) women with a prior history of PPT. Screening should occur at 6–12 wk postpartum. Women with Graves' disease who enter remission during pregnancy should be screened for recurrence by TSH assay at 3–6 months. USPSTF recommendation level: C; evidence, poor (2|⊕◯◯◯) (112–114) (see also Section 7).

8.1.–8.5. Background and evidence

Thyroid dysfunction (hypothyroidism, hyperthyroidism, and thyroid autoimmunity) during pregnancy can result in serious complications for both mother and infant (4, 6, 9, 131, 137). For women with undiagnosed thyroid disease, a screening test may identify dysfunction, allowing the institution of interventions such as levothyroxine therapy. The multitude of adverse outcomes linked to untreated thyroid disease during pregnancy (particularly relating to hypothyroidism) leads to consideration of the potential benefit and costs of screening for thyroid dysfunction before or during pregnancy.

The frequency of thyroid disease during pregnancy and postpartum is sufficient to support consideration for screening to detect abnormal TSH concentrations (19, 131, 137). Overt hypothyroidism occurs in 0.3–0.5% of pregnancies and SCH in 2–4% of pregnancies (5, 6, 9, 70, 72). Numerous studies document an adverse impact on pregnancy (and fetal well-being) when thyroid dysfunction (particularly hypothyroidism) or TPO antibodies are detected (5, 6, 9, 69, 70, 131). Optimal treatment of ma-

ternal overt hypothyroidism prevents these complications (9, 72, 139).

Maternal SCH is associated with increased incidence of adverse outcomes of pregnancy including preterm delivery, placental abruption, respiratory distress, early pregnancy loss, and admissions to the intensive care unit (4, 5, 21, 81, 137). Randomized, prospective study documents an increase in pregnancy complications among women with elevated serum TSH concentrations of 2.5–5.0 mIU/liter in the first trimester without TPO antibodies (138). These data are supported by other retrospective analysis (131). Correction of hypothyroidism before pregnancy restores the pregnancy outcomes to the rate seen in euthyroid TPO-Ab+ women (133, 139).

Although the majority of large-scale, well-designed studies depict a consistent adverse impact from mild to moderate maternal hypothyroidism, some studies are contradictory (9, 80). Noting that modest discordance exists in the published literature, the task force feels that the majority of available, high-quality data do support the finding that both subclinical and overt hypothyroidism increase the risk of adverse pregnancy outcomes.

Of separate concern, although of equal importance, is the potential for maternal hypothyroidism to also adversely affect fetal cognitive development. Several retrospective studies document danger to the developing fetal brain from both overt and subclinical maternal hypothyroidism (6, 22).

Two recent reports focus on the issue of treatment of SCH and screening. The primary endpoint of the report by Negro *et al.* (137) indicates that universal screening by 9 wk had no benefit on the overall outcome of the total screened *vs.* nonscreened populations. However, in their study individuals considered high risk were tested and treated in both populations. When the screened and detected "low-risk" pregnancies were compared with the low-risk hypothyroid patients diagnosed *after* pregnancy, there was a significant reduction in adverse outcomes. Still, it must be noted that screening was done at an early time (about 9 wk) and that the comparison groups had both SCH and positive anti-TPO-Ab.

Information on effects of screening and treatment in relation to neural development are sparse. Correction of iodine deficiency during pregnancy prevents adverse fetal neural development (see Section 6). In the "CATS" study recently published by Lazarus *et al.* (140), the overall outcomes on IQ testing at 3 yr of age between universally screened and not screened pregnancies were not significantly different. Importantly, assessment of maternal thyroid function in this study and initiation of levothyroxine when indicated occurred at 12 wk gestation or thereafter.

Two studies have assessed the efficacy of targeted screening of pregnant women for evidence of hypothyroidism. In the report of Vaidya *et al.* (133), 7.4% of "high-risk" pregnancies were found to have TSH above 4.2 mIU/liter. This represents 1.3% of the entire population studied. In this study, targeted screening failed to detect 28% of pregnancies with elevated TSH, representing 0.7% of the total population. Li *et al.* (81) found in a similar study that targeted screening missed 36% of all individuals with a TSH above 4.0 mIU/liter.

The complexity of how to interpret and effectively translate the above prospective investigations into clinical screening recommendations has led to mixed viewpoints among members of the task force. Some believe the data support a recommendation for universal screening of newly pregnant women by the ninth week or at the time of first visit. The Vaidya *et al.* (133) and Li *et al.* (81) studies suggest that universal screening is easily done, is reliable, has been deemed cost-effective in one published analysis, is already accepted in many practices and in some countries, but also that a targeted screening approach will fail to detect 30–40% of pregnancies with thyroid dysfunction and that targeted screening imposes the burden of an extended questionnaire, and possibly unreliable or incomplete data. The majority of committee members believed that although secondary endpoints suggest benefit in selected (TPO-Ab+) populations, the primary endpoints of both studies remain negative, and therefore a universal mandate for all women can be recommended neither for nor against at this time.

Regardless, there is unanimous task force agreement that targeted screening of high-risk women is recommended (Table 1) during the prenatal and perinatal periods. With this approach, the committee acknowledges the important data confirming that such case finding will unfortunately miss 30% or more of women with overt or subclinical hypothyroidism (133, 137).

Finally, women with known thyroid dysfunction and receiving levothyroxine deserve special attention prenatally. T_4 requirements increase 30–50% during gestation, beginning as early as 4–6 wk gestation (141). In women without residual thyroid function, exogenous levothyroxine must be increased at the time of pregnancy detection or hypothyroidism will occur. These data suggest that screening women with known thyroid dysfunction (receiving levothyroxine) for abnormal TSH concentrations *before* pregnancy is beneficial. Furthermore, women can be simultaneously counseled to increase their levothyroxine upon their first missed menstrual cycle and biochemical confirmation of pregnancy. A prospective trial confirms that a recommendation for a two-tablet-per-week increase of their baseline levothyroxine dose (nine

tablets per week instead of seven tablets) can substantially reduce the risk of maternal hypothyroidism during the first trimester (135).

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