

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

Leslie De Groot, Marcos Abalovich, Erik K. Alexander, Nobuyuki Amino, Linda Barbour, Rhoda H. Cobin, Creswell J. Eastman, John H. Lazarus, Dominique Luton, Susan J. Mandel, Jorge Mestman, Joanne Rovet, and Scott Sullivan

University of Rhode Island (L.D.-G.), Providence, Rhode Island 02881; Durand Hospital and Favaloro University (M.A.), C1078AAI Buenos Aires, Argentina; Brigham and Women's Hospital and Harvard Medical School (E.K.A.), Boston, Massachusetts 02115; Kuma Hospital (N.A.), Kobe 650-0011, Japan; University of Colorado School of Medicine (L.B.), Aurora, Colorado 80217; Mount Sinai School of Medicine (R.H.C.), New York, New York 10029; University of Sydney Medical School (C.J.E.), Sydney, NSW 2006, Australia; Cardiff University Medical School and University Hospital of Wales (J.H.L.), Cardiff CF14 4XW, United Kingdom; Hôpital Bichat and Beaujon Assistance Publique-Hôpitaux de Paris, Université Paris VII (D.L.), Paris 75018, France; University of Pennsylvania School of Medicine (S.J.M.), Philadelphia, Pennsylvania 19104; Keck School of Medicine, University of Southern California (J.M.), Los Angeles, California 90089; Hospital for Sick Children (J.R.), Toronto, Ontario, Canada M5G 1X8; and Medical University of South Carolina (S.S.), Charleston, South Carolina 29403

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)

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

Copyright © 2012 by The Endocrine Society

doi: 10.1210/jc.2011-2803 Received October 11, 2011. Accepted March 5, 2012.

For editorials see pages 2619, 2629, and 2632

This revised guideline replaces the previous version published in 2007: Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoe D, Mandel SJ, Stagnaro-Green A. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2007 Aug;92(8 Suppl):S1–S47.

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 $\mu\text{g/dl}$ 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 ¹³¹I 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. ¹³¹I 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 ¹³¹I 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 T₄ 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 T₄, or free T₄ index, or free T₄) 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 T₄ 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 T₃ 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 T₄ above the reference range or total T₄ > 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 T₄ or total T₄ 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 ¹³¹I 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 mea-

surement 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 T₃) 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 $\mu\text{g/dl}$ 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 $\mu\text{g/dl}$ 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 $\mu\text{g/d}$ for serum TSH levels between 5 and 10 mIU/liter, 50–75 $\mu\text{g/d}$ for serum TSH between 10 and 20 mIU/liter, and 75–100 $\mu\text{g/d}$ 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, pre-eclampsia, 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 Re-

porting 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-

perplacentalis 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 (1|⊕⊕○○) (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 T₄ or total T₄ 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 T₄ that do not cause overt hyperthyroidism.

Multiple studies have indicated that prior treatment with ¹³¹I 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 ¹³¹I 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 ¹³¹I 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 (1|⊕⊕⊕○○) (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 (2|⊕○○○○) (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 (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 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 $\mu\text{g}/\text{d}$ (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 $\mu\text{g}/\text{d}$ 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 $\mu\text{g}/\text{d}$ 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 $\mu\text{g}/\text{d}$ (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 $\mu\text{g}/\text{d}$) 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 $\mu\text{g}/\text{liter}$ 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 $\mu\text{g}/\text{liter}$ in 2002 and 160 $\mu\text{g}/\text{liter}$ in 2002–2004. Concomitantly, the mean urinary iodine in pregnant women in the United States decreased from 327 $\mu\text{g}/\text{liter}$ to 140 $\mu\text{g}/\text{liter}$ from 1971–1974 to 1988–1994, with an increase in the prevalence of moderately low urine iodine concentrations (<50 $\mu\text{g}/\text{liter}$) 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 $\mu\text{g}/\text{liter}$ (1988–1994), 173 $\mu\text{g}/\text{liter}$ (2001–2002), and 181 $\mu\text{g}/\text{liter}$ (2003–2004), but with a substantial number of women still having low urine iodine (21% < 100 $\mu\text{g}/\text{liter}$ and 4.7% < 50 $\mu\text{g}/\text{liter}$) 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 $\mu\text{g}/\text{liter}$.

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 levothy-

roxine. 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 non-selected 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 T₄ 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 T₃) 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. T₄ 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).

Acknowledgments

Address all correspondence and requests for reprints to: The Endocrine Society, 8401 Connecticut Avenue, Suite 900, Chevy Chase, Maryland 20815. E-mail: govt-prof@endo-society.org, Telephone: 301-941-0200. Address all commercial reprint requests for orders 101 and more to: Content Ed Net LLC, E-mail: ray.thibodeau@contentednet.com. Address all reprint requests for orders for 100 or fewer to Society Services, Telephone: 301-941-0210, E-mail: societyservices@endo-society.org, or Fax: 301-941-0257.

Co-Sponsoring Associations: Asia & Oceania Thyroid Association, European Thyroid Association, and Latin American Thyroid Society.

Financial Disclosures of the Task Force

Leslie De Groot, M.D. (chair)—Financial or Business/Organizational Interests: none disclosed; Significant Financial Interest or Leadership Position: none disclosed. **Marcos Abalovich, M.D.**—Financial or Business/Organizational Interests: American Thyroid Association Thyroid and Pregnancy Guidelines Task Force; Significant Financial Interest or Leadership: none disclosed. **Erik K. Alexander, M.D.**—Financial or Business/Organizational Interests: Veracyte, Inc.; Significant Financial Interest or Leadership Position: none disclosed. **Nobuyuki Amino, M.D.**—Financial or Business/Organizational Interests: none disclosed; Significant Financial Interest or Leadership: none disclosed. **Linda Barbour, MS, MSPH**—Financial or Business/Organizational Interests: none disclosed; Significant Financial Interest or Leadership Position: none disclosed. **Rhoda Cobin, M.D.**—Financial or Business/Organizational Interests: none disclosed; Significant Financial Interest or Leadership Position: none disclosed. **Creswell Eastman, M.D.**—Financial or Business/Organizational Interests: International Council on Iodine Deficiency and Disorders; Significant Financial Interest or Leadership Position: none disclosed. **John Lazarus, M.D.**—Financial or Business/Organizational Interests: British Thyroid Foundation, Abbott Labs, Merck-Serono; Significant Financial Interest or Leadership Position: none disclosed. **Dominique Luton, M.D.**—Financial or Business/Organizational Interests: none disclosed; Significant Financial Interest or Leadership Position: none disclosed. **Susan J. Mandel, M.D.**—Financial or Business/Organizational Interests: American Association of Clinical Endocrinology,

American Thyroid Association, Association of Program Directors in Endocrinology, Diabetes and Metabolism; Significant Financial Interest or Leadership Position: none disclosed. **Jorge Mestman, M.D.**—Financial or Business/Organizational Interests: American Thyroid Association; Significant Financial Interest or Leadership Position: none disclosed. **Joanne Rovet, Ph.D.**—Financial or Business/Organizational Interests: American Thyroid Association, Pediatric Endocrine Society; Significant Financial Interest or Leadership Position: none disclosed. **Scott Sullivan, M.D.**—Financial or Business/Organizational Interests: American Thyroid Association, American College of Gynecology; Significant Financial Interest or Leadership Position: none disclosed.

References

1. Demers LM, Spencer CA 2003 Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. *Clin Endocrinol (Oxf)* 58:138–140
2. Lee RH, Spencer CA, Mestman JH, Miller EA, Petrovic I, Braverman LE, Goodwin TM 2009 Free T4 immunoassays are flawed during pregnancy. *Am J Obstet Gynecol* 200:260.e1–e6
3. Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ 2004 Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. *Thyroid* 14:1084–1090
4. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG 2005 Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 105:239–245
5. Glinoe D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, Kinthaert J, Robijn C, Grun JP, de Nayer P 1991 Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. *J Clin Endocrinol Metab* 73:421–427
6. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ 1999 Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 341:549–555
7. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH 1993 Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 81:349–353
8. Man EB, Brown JF, Serunian SA 1991 Maternal hypothyroxinemia: psychoneurological deficits of progeny. *Ann Clin Lab Sci* 21:227–239
9. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O 2002 Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 12:63–68
10. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, LiVosli VA, Niccoli-Sire P, John R, Ruf J, Smyth PP, Spencer CA, Stockigt JR 2003 Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 13:3–126
11. Panesar NS, Li CY, Rogers MS 2001 Reference intervals for thyroid hormones in pregnant Chinese women. *Ann Clin Biochem* 38:329–332
12. Mandel SJ 2004 Hypothyroidism and chronic autoimmune thyroiditis in the pregnant state: maternal aspects. *Best Pract Res Clin Endocrinol Metab* 18:213–224

13. Kaplan MM 1992 Monitoring thyroxine treatment during pregnancy. *Thyroid* 2:147–152
14. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR 2004 Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 351:241–249
15. Loh JA, Wartofsky L, Jonklaas J, Burman KD 2009 The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. *Thyroid* 19:269–275
16. Sapin R, D'Herbomez M, Schlienger JL 2004 Free thyroxine measured with equilibrium dialysis and nine immunoassays decreases in late pregnancy. *Clin Lab* 50:581–584
17. Verga U, Bergamaschi S, Cortelazzi D, Ronzoni S, Marconi AM, Beck-Peccoz P 2009 Adjustment of L-T4 substitutive therapy in pregnant women with subclinical, overt or post-ablative hypothyroidism. *Clin Endocrinol (Oxf)* 70:798–802
18. Mandel SJ, Larsen PR, Seely EW, Brent GA 1990 Increased need for thyroxine during pregnancy in women with primary hypothyroidism. *N Engl J Med* 323:91–96
19. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, Mitchell ML 1991 Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 35:41–46
20. De Vivo A, Mancuso A, Giacobbe A, Moleti M, Maggio Savasta L, De Dominicis R, Priolo AM, Vermiglio F 2010 Thyroid function in women found to have early pregnancy loss. *Thyroid* 20:633–637
21. Williams GR 2008 Neurodevelopmental and neurophysiological actions of thyroid hormone. *J Neuroendocrinol* 20:784–794
22. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ 2003 Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)* 59:282–288
23. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H 2010 Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study. *J Clin Endocrinol Metab* 95:4227–4234
24. Mestman JH 2004 Hyperthyroidism in pregnancy. *Best Pract Res Clin Endocrinol Metab* 18:267–288
25. Goodwin TM, Montoro M, Mestman JH 1992 Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. *Am J Obstet Gynecol* 167:648–652
26. Tan JY, Loh KC, Yeo GS, Chee YC 2002 Transient hyperthyroidism of hyperemesis gravidarum. *BJOG* 109:683–688
27. Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K 1986 Anti-thyroid drug therapy for Graves' disease during pregnancy. Optimal regimen for fetal thyroid status. *N Engl J Med* 315:24–28
28. Mandel SJ, Cooper DS 2001 The use of antithyroid drugs in pregnancy and lactation. *J Clin Endocrinol Metab* 86:2354–2359
29. Cooper DS, Rivkees SA 2009 Putting propylthiouracil in perspective. *J Clin Endocrinol Metab* 94:1881–1882
30. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R 1999 Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet* 83:43–46
31. Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemine B, Addis A, Arnon J, Clementi M 2001 Adverse effects of prenatal methimazole exposure. *Teratology* 64:262–266
32. Johnsson E, Larsson G, Ljunggren M 1997 Severe malformations in infant born to hyperthyroid woman on methimazole. *Lancet* 350:1520
33. Martinez-Frias ML, Cereijo A, Rodriguez-Pinilla E, Urioste M 1992 Methimazole in animal feed and congenital aplasia cutis. *Lancet* 339:742–743
34. Greenberg F 1987 Choanal atresia and athelia: methimazole teratogenicity or a new syndrome? *Am J Med Genet* 28:931–934
35. Burrow GN 1985 The management of thyrotoxicosis in pregnancy. *N Engl J Med* 313:562–565
36. Stice RC, Grant CS, Gharib H, van Heerden JA 1984 The management of Graves' disease during pregnancy. *Surg Gynecol Obstet* 158:157–160
37. Brodsky JB, Cohen EN, Brown Jr BW, Wu ML, Whitcher C 1980 Surgery during pregnancy and fetal outcome. *Am J Obstet Gynecol* 138:1165–1167
38. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG 2006 Subclinical hyperthyroidism and pregnancy outcomes. *Obstet Gynecol* 107:337–341
39. Laurberg P, Nygaard B, Glinoe D, Grussendorf M, Orgiazzi J 1998 Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidence-based symposium organized by the European Thyroid Association. *Eur J Endocrinol* 139:584–586
40. Luton D, Le Gac I, Vuillard E, Castanet M, Guibourdenche J, Noel M, Toubert ME, Léger J, Boissinot C, Schlageter MH, Garel C, Tébké B, Oury JF, Czernichow P, Polak M 2005 Management of Graves' disease during pregnancy: the key role of fetal thyroid gland monitoring. *J Clin Endocrinol Metab* 90:6093–6098
41. Nachum Z, Rakover Y, Weiner E, Shalev E 2003 Graves' disease in pregnancy: prospective evaluation of a selective invasive treatment protocol. *Am J Obstet Gynecol* 189:159–165
42. Porreco RP, Bloch CA 1990 Fetal blood sampling in the management of intrauterine thyrotoxicosis. *Obstet Gynecol* 76:509–512
43. Berg GE, Nyström EH, Jacobsson L, Lindberg S, Lindstedt RG, Mattsson S, Niklasson CA, Norén AH, Westphal OG 1998 Radioiodine treatment of hyperthyroidism in a pregnant women. *J Nucl Med* 39:357–361
44. Bydder SA, Clarke J, Semmens J, Joseph DJ 2005 Genetic counselling following paternal therapeutic irradiation. *Australas Radiol* 49:119–121
45. Gorman CA 1999 Radioiodine and pregnancy. *Thyroid* 9:721–726
46. Lowe SA 2004 Diagnostic radiography in pregnancy: risks and reality. *Aust N Z J Obstet Gynaecol* 44:191–196
47. Zanzonico PB 1997 Radiation dose to patients and relatives incident to ¹³¹I therapy. *Thyroid* 7:199–204
48. McKenzie JM, Zakarija M 1992 Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid* 2:155–159
49. Mitsuda N, Tamaki H, Amino N, Hosono T, Miyai K, Tanizawa O 1992 Risk factors for developmental disorders in infants born to women with Graves disease. *Obstet Gynecol* 80:359–364
50. Mortimer RH, Tyack SA, Galligan JP, Perry-Keene DA, Tan YM 1990 Graves' disease in pregnancy: TSH receptor binding inhibiting immunoglobulins and maternal and neonatal thyroid function. *Clin Endocrinol (Oxf)* 32:141–152
51. Davidson KM, Richards DS, Schatz DA, Fisher DA 1991 Successful in utero treatment of fetal goiter and hypothyroidism. *N Engl J Med* 324:543–546
52. Fisher DA 1997 Fetal thyroid function: diagnosis and management of fetal thyroid disorders. *Clin Obstet Gynecol* 40:16–31
53. Polak M, Leger J, Luton D, Oury JF, Vuillard E, Boissinot C, Czernichow P 1997 Fetal cord blood sampling in the diagnosis and the treatment of fetal hyperthyroidism in the offsprings of a euthyroid mother, producing thyroid stimulating immunoglobulins. *Ann Endocrinol (Paris)* 58:338–342
54. Zimmerman D 1999 Fetal and neonatal hyperthyroidism. *Thyroid* 9:727–733
55. Mestman JH, Goodwin TM, Montoro MM 1995 Thyroid disorders of pregnancy. *Endocrinol Metab Clin North Am* 24:41–71
56. Huel C, Guibourdenche J, Vuillard E, Ouahba J, Piketty M, Oury JF, Luton D 2009 Use of ultrasound to distinguish between fetal hyperthyroidism and hypothyroidism on discovery of a goiter. *Ultrasound Obstet Gynecol* 33:412–420
57. Glinoe D 1998 Thyroid hyperfunction during pregnancy. *Thyroid* 8:859–864

58. Niswander KR, Gordon M, Berendes HW 1972 The women and their pregnancies. In: Niswander KR, Gordon M, eds. The collaborative perinatal study of the National Institute of Neurologic Disease and Stroke. Philadelphia: WB Saunders: 246–249
59. Glinoe D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, Kinthaert J, Lejeune B 1990 Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab* 71:276–287
60. Glinoe D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S 1993 Serum levels of intact human chorionic gonadotropin (HCG) and its free α - and β -subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest* 16: 881–888
61. Hershman JM 1999 Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. *Thyroid* 9:653–657
62. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH 1994 Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. *Obstet Gynecol* 84:946–949
63. Kempers MJ, van Tijn DA, van Trotsenburg AS, de Vijlder JJ, Wiedijk BM, Vulsma T 2003 Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. *J Clin Endocrinol Metab* 88:5851–5857
64. Papendieck P, Chiesa A, Prieto L, Gruñeiro-Papendieck L 2009 Thyroid disorders of neonates born to mothers with Graves' disease. *J Pediatr Endocrinol Metab* 22:547–553
65. Wenstrom KD, Weiner CP, Williamson RA, Grant SS 1990 Prenatal diagnosis of fetal hyperthyroidism using funipuncture. *Obstet Gynecol* 76:513–517
66. Rodien P, Brémont C, Sanson ML, Parma J, Van Sande J, Costagliola S, Luton JP, Vassart G, Duprez L 1998 Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. *N Engl J Med* 339: 1823–1826
67. Lazarus JH 1994 Thyroxine excess and pregnancy. *Acta Med Austriaca* 21:53–56
68. Lazarus JH 2005 Thyroid disorders associated with pregnancy: etiology, diagnosis, and management. *Treat Endocrinol* 4:31–41
69. De Carolis C, Greco E, Guarino MD, Perricone C, Dal Lago A, Giacomelli R, Fontana L, Perricone R 2004 Anti-thyroid antibodies and antiphospholipid syndrome: evidence of reduced fecundity and of poor pregnancy outcome in recurrent spontaneous aborters. *Am J Reprod Immunol* 52:263–266
70. Stagnaro-Green A, Roman SH, Cobin RH, el-Harazy E, Alvarez-Marfany M, Davies TF 1990 Detection of at-risk pregnancy by means of highly sensitive assays for thyroid autoantibodies. *JAMA* 264:1422–1425
71. Irvani AT, Saeedi MM, Pakraves J, Hamidi S, Abbasi M 2008 Thyroid autoimmunity and recurrent spontaneous abortion in Iran: a case-control study. *Endocr Pract* 14:458–464
72. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H 2006 Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* 91:2587–2591
73. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, Locorotondo G, Caroli P, Pezzarossa A, Dazzi D, Hassan H 2005 Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum Reprod* 20:1529–1533
74. Poppe K, Glinoe D, Tournaye H, Devroey P, van Steirteghem A, Kaufman L, Velkeniers B 2003 Assisted reproduction and thyroid autoimmunity: an unfortunate combination? *J Clin Endocrinol Metab* 88:4149–4152
75. Moosa M, Mazzaferri EL 1997 Outcome of differentiated thyroid cancer diagnosed in pregnant women. *J Clin Endocrinol Metab* 82:2862–2866
76. Debiève F, Dulière S, Bernard P, Hubinont C, De Nayer P, Daumetrie C 2009 To treat or not to treat euthyroid autoimmune disorder during pregnancy? *Gynecol Obstet Invest* 67:178–182
77. Vaquero E, Lazzarin N, De Carolis C, Valensise H, Moretti C, Ramanini C 2000 Mild thyroid abnormalities and recurrent spontaneous abortion: diagnostic and therapeutical approach. *Am J Reprod Immunol* 43:204–208
78. Al-Kunani AS, Knight R, Haswell SJ, Thompson JW, Lindow SW 2001 The selenium status of women with a history of recurrent miscarriage. *BJOG* 108:1094–1097
79. Gärtner R, Gasnier BC, Dietrich JW, Krebs B, Angstwurm MW 2002 Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. *J Clin Endocrinol Metab* 87:1687–1691
80. Männistö T, Väärämäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, Bloigu A, Järvelin MR, Savanto-Luukkonen E 2009 Perinatal outcome of children born to mothers with thyroid dysfunction or antibodies: a prospective population-based cohort study. *J Clin Endocrinol Metab* 94:772–779
81. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, Teng X, Guo R, Wang H, Li J, Chen Y, Wang W, Chawinga M, Zhang L, Yang L, Zhao Y, Hua T 2010 Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clin Endocrinol (Oxf)* 72:825–829
82. Kung AW, Chau MT, Lao TT, Tam SC, Low LC 2002 The effect of pregnancy on thyroid nodule formation. *J Clin Endocrinol Metab* 87:1010–1014
83. Mazzaferri EL, Jhiang SM 1994 Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med* 97:418–428
84. Vini L, Hyer S, Pratt B, Harmer C 1999 Management of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol* 140:404–406
85. Herzon FS, Morris DM, Segal MN, Rauch G, Parnell T 1994 Co-existent thyroid cancer and pregnancy. *Arch Otolaryngol Head Neck Surg* 120:1191–1193
86. Rosen IB, Korman M, Walfish PG 1997 Thyroid nodular disease in pregnancy: current diagnosis and management. *Clin Obstet Gynecol* 40:81–89
87. Choe W, McDougall IR 1994 Thyroid cancer in pregnant women: diagnostic and therapeutic management. *Thyroid* 4:433–435
88. Chow SM, Yau S, Lee SH, Leung WM, Law SC 2004 Pregnancy outcome after diagnosis of differentiated thyroid carcinoma: no deleterious effect after radioactive iodine treatment. *Int J Radiat Oncol Biol Phys* 59:992–1000
89. Schlumberger M, De Vathaire F, Ceccarelli C, Francese C, Pinchera A, Parmentier C 1995 Outcome of pregnancy in women with thyroid carcinoma. *J Endocrinol Invest* 18:150–151
90. Marley EF, Oertel YC 1997 Fine-needle aspiration of thyroid lesions in 57 pregnant and postpartum women. *Diagn Cytopathol* 16:122–125
91. Cooper DS, Doherty GM, Haugen BR, Hauger BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM 2009 Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 19:1167–1214
92. Yasmien S, Cress R, Romano PS, Xing G, Berger-Chen S, Daniels B, Smith LH 2005 Thyroid cancer in pregnancy. *Int J Gynaecol Obstet* 91:15–20
93. Sam S, Molitch ME 2003 Timing and special concerns regarding endocrine surgery during pregnancy. *Endocrinol Metab Clin North Am* 32:337–354
94. Vannucchi G, Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, Beck-Peccoz P, Fugazzola L 2010 Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. *Eur J Endocrinol* 162:145–151
95. Leboeuf R, Emerick LE, Martorella AJ, Tuttle RM 2007 Impact of pregnancy on serum thyroglobulin and detection of recurrent dis-

- ease shortly after delivery in thyroid cancer survivors. *Thyroid* 17:543–547
96. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, Straus S, Thabane L, Gafni A, Ezzat S, George SR, Goldstein DP 2008 A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. *Clin Endocrinol (Oxf)* 69:479–490
 97. Andersson M, de Benoist B, Delange F, Zupan J 2007 Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* 10:1606–1611
 98. Glinoe D 1997 Maternal and fetal impact of chronic iodine deficiency. *Clin Obstet Gynecol* 40:102–116
 99. Hollowell JG, Haddow JE 2007 The prevalence of iodine deficiency in women of reproductive age in the United States of America. *Public Health Nutr* 10:1532–1539; discussion 1540–1541
 100. Glinoe D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grün JP, Kinthaert J, Lejeune B 1995 A randomized trial for the treatment of mild iodine deficiency during pregnancy: maternal and neonatal effects. *J Clin Endocrinol Metab* 80:258–269
 101. Chaouki ML, Benmiloud M 1994 Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. *Eur J Endocrinol* 130:547–551
 102. Liesenkötter KP, Göpel W, Bogner U, Stach B, Grüters A 1996 Earliest prevention of endemic goiter by iodine supplementation during pregnancy. *Eur J Endocrinol* 134:443–448
 103. Nøhr SB, Laurberg P 2000 Opposite variations in maternal and neonatal thyroid function induced by iodine supplementation during pregnancy. *J Clin Endocrinol Metab* 85:623–627
 104. Romano R, Jannini EA, Pepe M, Grimaldi A, Olivieri M, Spennati P, Cappa F, D'Armiento M 1991 The effects of iodoprophylaxis on thyroid size during pregnancy. *Am J Obstet Gynecol* 164:482–485
 105. Delange F 2004 Optimal iodine nutrition during pregnancy, lactation and the neonatal period. *Int J Endocrinol Metab* 2:1–12
 106. Becks GP, Burrow GN 1991 Thyroid disorders and pregnancy. *Med Clin North Am* 75:121–150
 107. Campbell N, Dary O, Cappuccio FP, Neufeld LM, Harding KB, Zimmermann MB 2012 Collaboration to optimize dietary intakes of salt and iodine: a critical but overlooked public health issue. *Bull World Health Organ* 90:73–74
 108. Pérez-López FR 2007 Iodine and thyroid hormones during pregnancy and postpartum. *Gynecol Endocrinol* 23:414–428
 109. Caldwell KL, Miller GA, Wang RY, Jain RB, Jones RL 2008 Iodine status of the U.S. population, National Health and Nutrition Examination Survey 2003–2004. *Thyroid* 18:1207–1214
 110. Vermiglio F, Sidoti M, Finocchiaro MD, Battiato S, Lo Presti VP, Benvenega S, Trimarchi F 1990 Defective neuromotor and cognitive ability in iodine-deficient schoolchildren of an endemic goiter region in Sicily. *J Clin Endocrinol Metab* 70:379–384
 111. Muller AF, Drexhage HA, Berghout A 2001 Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care. *Endocr Rev* 22:605–630
 112. Stagnaro-Green A 2002 Clinical review 152: postpartum thyroiditis. *J Clin Endocrinol Metab* 87:4042–4047
 113. Premawardhana LD, Parkes AB, John R, Harris B, Lazarus JH 2004 Thyroid peroxidase antibodies in early pregnancy: utility for prediction of postpartum thyroid dysfunction and implications for screening. *Thyroid* 14:610–615
 114. Alvarez-Marfany M, Roman SH, Drexler AJ, Robertson C, Stagnaro-Green A 1994 Long-term prospective study of postpartum thyroid dysfunction in women with insulin dependent diabetes mellitus. *J Clin Endocrinol Metab* 79:10–16
 115. Gerstein HC 1993 Incidence of postpartum thyroid dysfunction in patients with type I diabetes mellitus. *Ann Intern Med* 118:419–423
 116. McCanlies E, O'Leary LA, Foley TP, Kramer MK, Burke JP, Libman A, Swan JS, Steenkiste AR, McCarthy BJ, Trucco M, Dorman JS 1998 Hashimoto's thyroiditis and insulin-dependent diabetes mellitus: differences among individuals with and without abnormal thyroid function. *J Clin Endocrinol Metab* 83:1548–1551
 117. Azizi F 2005 The occurrence of permanent thyroid failure in patients with subclinical postpartum thyroiditis. *Eur J Endocrinol* 153:367–371
 118. Othman S, Phillips DI, Parkes AB, Richards CJ, Harris B, Fung H, Darke C, John R, Hall R, Lazarus JH 1990 A long-term follow-up of postpartum thyroiditis. *Clin Endocrinol (Oxf)* 32:559–564
 119. Tachi J, Amino N, Tamaki H, Aozasa M, Iwatani Y, Miyai K 1988 Long term follow-up and HLA association in patients with postpartum hypothyroidism. *J Clin Endocrinol Metab* 66:480–484
 120. Cox JL, Murray D, Chapman G 1993 A controlled study of the onset, duration and prevalence of postnatal depression. *Br J Psychiatry* 163:27–31
 121. Harris B, Othman S, Davies JA, Weppner GJ, Richards CJ, Newcombe RG, Lazarus JH, Parkes AB, Hall R, Phillips DI 1992 Association between postpartum thyroid dysfunction and thyroid antibodies and depression. *BMJ* 305:152–156
 122. Kent GN, Stuckey BG, Allen JR, Lambert T, Gee V 1999 Postpartum thyroid dysfunction: clinical assessment and relationship to psychiatric affective morbidity. *Clin Endocrinol (Oxf)* 51:429–438
 123. Kuijpers JL, De Hann-Meulman M, Vader HL, Pop VJ, Wiersinga WM, Drexhage HA 1998 Cell-mediated immunity and postpartum thyroid dysfunction: a possibility for the prediction of disease? *J Clin Endocrinol Metab* 83:1959–1966
 124. Lucas A, Pizarro E, Granada ML, Salinas I, Foz M, Sanmarti A 2000 Postpartum thyroiditis: epidemiology and clinical evolution in a nonselected population. *Thyroid* 10:71–77
 125. Stamp GE, Crowther CA 1994 Postnatal depression: a South Australian prospective survey. *Aust N Z J Obstet Gynaecol* 34:164–167
 126. Cleare AJ, McGregor A, Chambers SM, Dawling S, O'Keane V 1996 Thyroxine replacement increases central 5-hydroxytryptamine activity and reduces depressive symptoms in hypothyroidism. *Neuroendocrinology* 64:65–69
 127. Stagnaro-Green A 2004 Postpartum thyroiditis. *Best Pract Res Clin Endocrinol Metab* 18:303–316
 128. Amino N, Tada H, Hidaka Y 1999 Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. *Thyroid* 9:705–713
 129. Amino N, Mori H, Iwatani Y, Tanizawa O, Kawashima M, Tsuge I, Ibaragi K, Kumahara Y, Miyai K 1982 High prevalence of transient post-partum thyrotoxicosis and hypothyroidism. *N Engl J Med* 306:849–852
 130. Hidaka Y, Tamaki H, Iwatani Y, Tada H, Mitsuda N, Amino N 1994 Prediction of post-partum Graves' thyrotoxicosis by measurement of thyroid stimulating antibody in early pregnancy. *Clin Endocrinol (Oxf)* 41:15–20
 131. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ 2000 Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 7:127–130
 132. Glinoe D, Riahi M, Grün JP, Kinthaert J 1994 Risk of subclinical hypothyroidism in pregnant women with asymptomatic autoimmune thyroid disorders. *J Clin Endocrinol Metab* 79:197–204
 133. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, Bilous R 2007 Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 92:203–207
 134. Abalovich M, Alcaraz G, Kleiman-Rubinshtein J, Pavlove MM, Cornelio C, Levalle O, Gutierrez S 2010 The relationship of preconception TSH levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. *Thyroid* 20:1175–1178

135. Yassa L, Marqusee E, Fawcett R, Alexander EK 2010 Thyroid Hormone Early Adjustment in Pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 95:3234–3241
136. Rotondi M, Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Amato G, Carella C 2004 Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. *Eur J Endocrinol* 151:695–700
137. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A 2010 Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 95:1699–1707
138. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A 2010 Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab* 95:E44–E48
139. Tan TO, Cheng YW, Caughey AB 2006 Are women who are treated for hypothyroidism at risk for pregnancy complications? *Am J Obstet Gynecol* 194:e1–e3
140. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, Chiusano E, John R, Guaraldo V, George LM, Perona M, Dall'Amico D, Parkes AB, Joomun M, Wald NJ 2012 Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 366:493–501
141. Stricker R, Echenard M, Eberhart R, Chevailler MC, Perez V, Quinn FA, Stricker R 2007 Evaluation of maternal thyroid function during pregnancy: the importance of using gestational age-specific reference intervals. *Eur J Endocrinol* 157:509–514



**Save the Date for Clinical Endocrinology Update,
September 13-15, 2012, Miami, Florida.**

www.endo-society.org/CEU