CLINICAL PRACTICE GUIDELINE

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

Marcos Abalovich, Nobuyuki Amino, Linda A. Barbour, Rhoda H. Cobin, Leslie J. De Groot, Daniel Glinoer, Susan J. Mandel, and Alex Stagnaro-Green

Endocrinology Division (M.A.), Durand Hospital, Buenos Aires, Argentina; Center for Excellence in Thyroid Care (N.A.), Kuma Hospital, Kobe 650-0011, Japan; Divisions of Endocrinology and Maternal-Fetal Medicine (L.A.B.), University of Colorado at Denver and Health Sciences Center, Aurora, Colorado 80010; The Mount Sinai School of Medicine (R.H.C.), New York, New York 10016; Department of Medicine (L.J.D.G.), Division of Endocrinology, Brown University, Providence Rhode Island 02903; Endocrine Division (D.G.), University Hospital Saint Pierre, B-1000 Brussels, Belgium; Division of Endocrinology, Diabetes, and Metabolism (S.J.M.), University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104; Departments of Medicine and Obstetrics, Gynecology, and Women's Health (A.S.-G.), University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey 07101; and Touro University College of Medicine (A.S.-G.), Hackensack, New Jersey 07601

Objective: The objective is to provide clinical guidelines for the management of thyroid problems present during pregnancy and in the postpartum.

Participants: The Chair was selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society. The Chair requested participation by the Latin American Thyroid Society, the Asia and Oceania Thyroid Society, the American Thyroid Association, the European Thyroid Association, and the American Association of Clinical Endocrinologists, and each organization appointed a member to the task force. Two members of The Endocrine Society were also asked to participate. The group worked on the guidelines for 2 yr and held two meetings. There was no corporate funding, and no members received remuneration.

Evidence: Applicable published and peer-reviewed literature of the last two decades was reviewed, with a concentration on original investigations. The grading of evidence was done using the United States Preventive Services Task Force system and, where possible, the GRADE system.

Consensus Process: Consensus was achieved through conference calls, two group meetings, and exchange of many drafts by E-mail. The manuscript was reviewed concurrently by the Society's CGS, Clinical Affairs Committee, members of The Endocrine Society, and members of each of the collaborating societies. Many valuable suggestions were received and incorporated into the final document. Each of the societies endorsed the guidelines.

Conclusions: Management of thyroid diseases during pregnancy requires special considerations because pregnancy induces major changes in thyroid function, and maternal thyroid disease can have adverse effects on the pregnancy and the fetus. Care requires coordination among several healthcare professionals. Avoiding maternal (and fetal) hypothyroidism is of major importance because of potential damage to fetal neural development, an increased incidence of miscarriage, and preterm delivery. Maternal hyperthyroidism and its treatment may be accompanied by coincident problems in fetal thyroid function. Autoimmune thyroid disease is associated with both increased rates of miscarriage, for which the appropriate medical response is uncertain at this time, and postpartum thyroiditis. Fine-needle aspiration cytology should be performed for dominant thyroid nodules discovered in pregnancy. Radioactive isotopes must be avoided during pregnancy and lactation. Universal screening of pregnant women for thyroid disease is not yet supported by adequate studies, but case finding targeted to specific groups of patients who are at increased risk is strongly supported. (*J Clin Endocrinol Metab* **92:** S1–S47, 2007)

EXECUTIVE SUMMARY

OVER THE PAST 15 yr there has been a rapid expansion of knowledge regarding thyroid disease and pregnancy. These advances relate to the optimal management of pregnant women on levothyroxine therapy, the impact of iodine deficiency on the mother and developing fetus, the adverse effect of maternal hypothyroidism on mental devel-

opment in their infants, the syndrome of postpartum thyroiditis (PPT), and its relation to permanent hypothyroidism. Furthermore, a doubling of the miscarriage rate has been reported in studies in antibody-positive euthyroid women, and an increase in preterm delivery has been found in women with subclinical hypothyroidism and/or thyroid autoimmunity.

Given the rapidity of advances in this field, it is not surprising that controversy surrounds optimal detection and management of thyroid disease in the pregnant woman. Thyroid disease during pregnancy has certain characteristics that make writing guidelines more complicated than for some other fields. This field 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 unsatisfactory iodine nutrition. Pregnancy may affect the course of these thyroid disorders, and conversely, thyroid diseases may affect the course of pregnancy. Moreover, 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.

METHODS

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. Members of the task force included representatives from The Endocrine Society, American Thyroid Association, Association of American Clinical Endocrinologists, European Thyroid Association, Asia and Oceania Thyroid Association, and the Latin American Thyroid Society. The task force worked during 2 yr to develop the guidelines, had multiple phone conversations, and two 2-d retreats. Upon completion of the guidelines, they were reviewed and approved by all of the participants.

Our committee undertook to review 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 supplementation, only two prospective, randomized intervention trials have been published in this area. We are aware of two large-scale prospective intervention trials that are presently ongoing. Nevertheless, in the last 15 yr, many high-quality studies have modified older dogmas and profoundly changed the ways in which these patients are managed. These studies are most often prospective or retrospective clinical evaluations of a particular patient population and matched groups of control women. Such studies, when carefully performed, adequately matched, and appropriately interpreted, provide the bulk of the evidence presented herein.

The committee evaluated recommendations and evidence using the methodology of the United States Preventive Service Task Force (USPSTF), in which treatments or medical advice are referred to as a "service." The USPSTF grades its recommendations (level A, B, C, D, or I) on the basis of the strength of evidence and magnitude of net benefit (benefits minus harms), as follows.

A. The USPSTF strongly recommends that clinicians provide (the service) to eligible patients. *The USPSTF found good evidence that (the service) improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians provide (the service) to eligible patients. *The USPSTF found at least fair evidence that (the service) improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of (the service). *The USPSTF found at least fair evidence that (the service) can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*

D. The USPSTF recommends against routinely providing (the service) to asymptomatic patients. *The USPSTF found good evidence that (the service) is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing (the service). *Evidence that (the service) is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

The USPSTF grades the quality of the overall evidence for a service on a three-point scale (good, fair, or poor), defined as follows:

Good: Evidence includes consistent results from well designed, well conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

In addition to the USPSTF grading of recommendations, we have also included the appropriate recommendation level as indicated by the GRADE system. The value of an evidence-based recommendation, using the GRADE system, is scored from strong to moderate (1–2) and accompanied by symbols indicating the value of the evidence: high (1, $\oplus\oplus\oplus\oplus$ or $\oplus\oplus\oplus\bigcirc$), moderate (2, $\oplus\oplus\bigcirc\bigcirc$), low ($\oplus\bigcirc\bigcirc\bigcirc$), and very low ($\bigcirc\bigcirc\bigcirc\bigcirc$). (There are no equivalents in the GRADE system for the recommendation levels C, D, and I used in the USPSTF system.)

The supporting data for the full committee report follow this executive summary. The supporting data consist of eight subsections dealing in detail with specific maternal/fetal thyroid problems. Each subsection provides the related background and evidence for recommendations. In the subsection reports, we have indicated specific bibliographic citations on which each recommendation is based, and for each

report cited as evidence for a given recommendation, a short summary is provided. We believe that this approach provides an important direct link between the supporting evidence and the recommendation.

BACKGROUND AND EVIDENCE

The complete discussion of background data and evidence is offered in the supporting data that follow this executive summary. Some important issues are noted here.

Pregnant and lactating women require additional iodine intake, whether in iodine-poor or iodine-sufficient countries. The recommended average iodine intake is approximately 250 μg/d (1). Severe iodine deficiency, if inadequately treated, is a major cause of neurological damage worldwide (2).

Both overt and subclinical hypothyroidism have adverse effects on the course of pregnancy and development of the fetus (3–5). Hypothyroidism should be corrected before initiation of pregnancy, replacement dosage should be augmented early in pregnancy (6), and euthyroidism should be maintained throughout. Overt maternal hypothyroidism has been associated with damage to fetal intellectual development (7), presumably because of inadequate transplacental supply of hormone during early pregnancy (8). Whether subclinical hypothyroidism carries this risk remains unproven, but replacement therapy for this condition is nonetheless advised.

Propylthiouracil is recommended as the first-line drug for treatment of hyperthyroidism during pregnancy, because of the probable association of methimazole with fetal developmental abnormalities (9, 10). Maternal Graves' disease, past or present, carries a risk for the pregnancy and for the fetus. Antithyroid drug (ATD) therapy to the mother can induce fetal hypothyroidism, and transplacental passage of TSH-receptor antibodies (TRAb) can cause fetal hyperthyroidism (11–13). Targeting ATD treatment to maintain maternal serum free T_4 levels at the upper limit of the nonpregnant T_4 range usually protects the fetus from hypothyroidism (14). Close following of maternal T_4 and TSH levels, assay of TRAb, and fetal ultrasonography including the thyroid are recommended for guiding therapy (15), and fetal blood sampling is rarely needed (15, 16). Fetal hyperthyroidism does not occur during pregnancies in which TRAb levels are normal and ATD is not administered. Surgery may be required in some instances. Propylthiouracil, propranolol, and iodides may be used for preoperative preparation.

Hyperemesis is associated with elevation of thyroid hormone levels above average pregnancy values and suppression of TSH (17–19). Occasionally, patients are clinically thyrotoxic. The elevation of thyroid hormone levels and gestational hyperthyroidism are typically self-remitting and in most cases do not require antithyroid treatment (17, 20). Subclinical hyperthyroidism, commonly found in this setting, does not require therapy, and therapy is advised against because it might induce fetal hypothyroidism (21).

Thyroid nodules recognized during pregnancy, or growing, are typically biopsied under ultrasound guidance (22, 23), and if appropriate, surgery is performed in the mid-trimester (24). Delay in treatment of low-grade tumors until

after delivery is not considered a danger (25). Pregnancy is not thought to adversely affect the course of thyroid malignancy (26–28). TSH suppression for known thyroid malignancy may be maintained during pregnancy with detectable TSH and with T_4 at the upper end of the range for normal pregnancy. Radioactive iodine (RAI) must not be administered during pregnancy or lactation.

Autoimmune thyroid disease is common in pregnancy. The presence of antibodies to thyroid peroxidase or thyroglobulin is associated with a significant increment in miscarriages (29, 30). One prospective study has reported that treatment with T_4 during pregnancy may reverse this risk (31). Additional studies on this important issue are needed.

PPT, a form of autoimmune thyroid disease closely related to Hashimoto's thyroiditis, is found in about 7% of women in the postpartum period (32). It causes hyperthyroidism and/or hypothyroidism that is usually transient (but often seriously symptomatic) (33, 34) and increases the risk of later permanent hypothyroidism (35, 36). Although depression may be a symptom of hypothyroidism in any setting, PPT *per se* has not been clearly linked to postpartum depression (37, 38).

A major unsettled question is the advisability of universal screening of pregnant women for thyroid disease, through TSH testing, and possibly antibody testing. The prevalence of overt thyroid disease in this population is 1%, and there is also a 2–3% prevalence of subclinical hypothyroidism and 10–15% antibody positivity (30, 39). As of this date, only one study has demonstrated that treatment of antibody positive euthyroid women with T_4 decreases the rate of miscarriage and preterm delivery (31). Thus, for now, the committee recommends targeted case finding during early pregnancy but anticipates that ongoing studies may alter this recommendation (40). Vaidya *et al.* (41) recently reported a study of screening by means of TSH, T_4, free T_4, and thyroid peroxidase antibodies in 1560 consecutive pregnant women. An important result was that screening only women considered high risk on the basis of a personal or family history of thyroid disease or a history of other autoimmune disease would have missed 30% of women with overt or subclinical hypothyroidism.

RECOMMENDATIONS

1. HYPOTHYROIDISM AND PREGNANCY: MATERNAL AND FETAL ASPECTS

1.1.1. Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus. Therefore maternal hypothyroidism should be avoided. USPSTF recommendation level is A; evidence is fair (GRADE 1|⊕⊕⊕○). Targeted case finding is recommended at the first prenatal visit or at diagnosis of pregnancy (see *Section 8, Screening for thyroid dysfunction during pregnancy*). USPSTF recommendation level is B; evidence is fair (GRADE 2|⊕⊕○○).

1.1.2. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception T_4 dose to reach a TSH level not higher than 2.5 μU/ml before pregnancy. USPSTF recommendation level is I; evidence is poor (⊕○○○).

1.1.3. The T_4 dose usually needs to be incremented by 4–6

wk gestation and may require a 30–50% increase in dosage. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

1.1.4. If overt hypothyroidism is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. The T_4 dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 μU/ml in the first trimester (or 3 μU/ml in the second and third trimesters) or to trimester-specific normal TSH ranges. Thyroid function tests should be remeasured within 30–40 d. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

1.1.5. 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. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕○).

1.1.6. Subclinical hypothyroidism (serum TSH concentration above the upper limit of the reference range with a normal free T_4) has been shown to be associated with an adverse outcome for both the mother and offspring. T_4 treatment has been shown to improve obstetrical outcome but 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 subclinical hypothyroidism. For obstetrical outcome, USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○). For neurological outcome, USPSTF recommendation level is I; evidence is poor (○○○○).

1.1.7. After delivery, most hypothyroid women need a decrease in the T_4 dosage they received during pregnancy. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

2. MANAGEMENT OF MATERNAL HYPERTHYROIDISM: MATERNAL (A) AND FETAL (B) ASPECTS

2.1.a.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by evidence of autoimmunity, a goiter, and presence of TRAb. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

2.1.a.2. For overt hyperthyroidism due to Graves' disease or hyperfunctioning thyroid nodules, ATD therapy should be either initiated (for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T_4 in the upper nonpregnant reference range. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

2.1.a.3. Because available evidence suggests methimazole may be associated with congenital anomalies, propylthiouracil should be used as a first-line drug, if available, especially during first-trimester organogenesis. Methimazole may be prescribed if propylthiouracil is not available or if a patient cannot tolerate or has an adverse response to pro-

pylthiouracil. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○).

2.1.a.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, or 3) a patient is not adherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. USPSTF recommendation level is I; evidence is poor (⊕○○○).

2.1.a.5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. USPSTF recommendation level is I; evidence is poor (⊕○○○).

2.1.b.1 TRAb (either TSH receptor-stimulating or -binding antibodies) freely cross the placenta and can stimulate the fetal thyroid. These antibodies should be measured before pregnancy or by the end of the second trimester in mothers with current Graves' disease, with a history of Graves' disease and treatment with ^{131}I or thyroidectomy, or with a previous neonate with Graves' disease. 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 is B; evidence is fair (GRADE 1|⊕⊕⊕○).

2.1.b.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 is A; evidence is good (GRADE 1|⊕⊕⊕⊕). There are no data for or against recommending termination of pregnancy after ^{131}I exposure. USPSTF recommendation level is I; evidence is poor (⊕○○○).

2.1.b.3. In women with elevated TRAb or in women treated with ATD, fetal ultrasound should be performed to look for evidence of fetal thyroid dysfunction that could include growth restriction, hydrops, presence of goiter, or cardiac failure. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○).

2.1.b.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and if the information gained would change the treatment. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○).

2.1.b.5. All newborns of mothers with Graves' disease should be evaluated for thyroid dysfunction and treated if necessary. USPSTF recommendation level is B; evidence is fair (GRADE 2|⊕○○○).

3. GESTATIONAL HYPEREMESIS AND HYPERTHYROIDISM

3.1. Thyroid function tests should be measured in all patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria) USPSTF recommendation level is B; evidence is poor (GRADE 2|⊕○○○).

3.2. Few women with hyperemesis gravidarum will require ATD treatment. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕). Overt hyperthyroidism believed due to coincident Graves' disease should be treated with ATD. USPSTF recommendation level is B; evidence is

fair (GRADE 1|⊕⊕⊕○). Gestational hyperthyroidism with clearly elevated thyroid hormone levels (free T_4 above the reference range or total $T_4 > 150\%$ of top normal pregnancy value and TSH < 0.1 μU/ml) and evidence of hyperthyroidism may require treatment as long as clinically necessary. USPSTF recommendation level is I; evidence is poor (⊕○○○).

4. AUTOIMMUNE THYROID DISEASE AND MISCARRIAGE

4.1. Although 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 this date, only one adequately designed intervention trial has demonstrated a decrease in the miscarriage rate in thyroid antibody-positive euthyroid women. USPSTF recommendation level is C; evidence is fair (GRADE 2|⊕○○○).

5. THYROID NODULES AND CANCER

5.1. Fine-needle aspiration (FNA) cytology should be performed for thyroid nodules larger than 1 cm discovered in pregnancy. Ultrasound-guided FNA may have an advantage for minimizing inadequate sampling. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○).

5.2. When nodules are discovered in the first or early second trimester to be malignant on cytopathological analysis or exhibit rapid growth, pregnancy should not be interrupted, but surgery should be offered in the second trimester before fetal viability. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease 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 surgical treatment soon after delivery is unlikely to adversely affect prognosis. USPSTF recommendation level is B; evidence is fair (GRADE 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 or an FNA positive for or suspicious for cancer and those who elect to delay surgical treatment until postpartum. High-risk patients may benefit from a greater degree of TSH suppression compared with low-risk patients. The free T_4 or total T_4 levels should ideally not be increased above the normal range for pregnancy. USPSTF recommendation level is I; evidence is poor (⊕○○○).

5.4. RAI administration with ^{131}I should not be given to women who are breastfeeding. USPSTF recommendation level is B; evidence is fair (GRADE 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 is B; evidence is fair (GRADE 1|⊕⊕○○).

6. IODINE NUTRITION DURING PREGNANCY

6.1. Women of childbearing age should have an average iodine intake of 150 μg/d. During pregnancy and breast-feeding, women should increase their daily iodine intake to 250 μg on average. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕○).

6.2. Iodine intake during pregnancy and breastfeeding should not exceed twice the daily recommended nutritional intake for iodine, *i.e.* 500 μg iodine per day. USPSTF recommendation level is I; evidence is poor (⊕○○○).

6.3. To assess the adequacy of the iodine intake during pregnancy in a population, urinary iodine concentration should be measured in a cohort of the population. Urinary iodine concentration should ideally range between 150 and 250 μg/liter. USPSTF recommendation level is A; evidence is good (GRADE 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 an established USI program where the coverage is known to be only partial, and finally 3) remote areas with no accessible USI program and difficult socioeconomic conditions. USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕).

7. POSTPARTUM THYROIDITIS

7.1. There are insufficient data to recommend screening of all women for PPT. USPSTF recommendation level is I; evidence is poor (⊕○○○).

7.2. Women known to be thyroid peroxidase antibody positive should have a TSH performed at 3 and 6 months postpartum USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕○).

7.3. The prevalence of PPT in women with type 1 diabetes is 3-fold greater than in the general population. Postpartum screening (TSH determination) is recommended for women with type 1 diabetes mellitus at 3 and 6 months postpartum. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○).

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 is A; evidence is good (GRADE 1|⊕⊕⊕○).

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

7.6. There is insufficient evidence to conclude whether an association exists between postpartum depression and either PPT or thyroid antibody positivity (in women who did not develop PPT). USPSTF recommendation level is I; evidence is poor (○○○○).

However, because hypothyroidism is a potentially revers-

ible cause of depression, women with postpartum depression should be screened for hypothyroidism and appropriately treated. USPSTF recommendation level is B; evidence is fair (GRADE 2|⊕⊕◯◯).

8. SCREENING FOR THYROID DYSFUNCTION DURING PREGNANCY

Although the benefits of universal screening for thyroid dysfunction (primarily hypothyroidism) may not be justified by the current evidence (presented above), we recommend case finding among the following groups of women at high risk for thyroid disease by measurement of TSH:

1. Women with a history of hyperthyroid or hypothyroid disease, PPT, or thyroid lobectomy.

2. Women with a family history of thyroid disease.

3. Women with a goiter.

4. Women with thyroid antibodies (when known).

5. Women with symptoms or clinical signs suggestive of thyroid underfunction or overfunction, including anemia, elevated cholesterol, and hyponatremia.

6. Women with type I diabetes.

7. Women with other autoimmune disorders.

8. Women with infertility who should have screening with TSH as part of their infertility work-up.

9. Women with previous therapeutic head or neck irradiation.

10. Women with a history of miscarriage or preterm delivery. USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕◯◯).

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Subsection Reports

SECTION 1. MANAGEMENT OF HYPOTHYROIDISM: MATERNAL AND FETAL ASPECTS

1.2. BACKGROUND

1.2.1. Clinical epidemiology and causal factors. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3–0.5% for overt hypothyroidism (OH) and 2–3% for subclinical hypothyroidism (SCH). Thyroid autoantibodies are found in 5–15% of women in the childbearing age, and chronic autoimmune thyroiditis is the main cause of hypothyroidism during pregnancy (1–5). As an example, in a prospective population study of 9471 pregnant women in the United States in whom serum TSH was measured during the second trimester, hypothyroidism was diagnosed in 2.2% of the cohort and autoimmune thyroiditis was present in 55% of women with SCH and more than 80% in women with OH (2). Other causes of thyroid insufficiency include the treatment of hyperthyroidism (using radioiodine ablation or surgery) or surgery for thyroid tumors. A hypothalamic-hypophyseal origin of hypothyroidism is rare and can include lymphocytic hypophysitis occurring during pregnancy or postpartum (3). It is important to remember, however, that on a worldwide basis the most important cause of thyroid insufficiency remains iodine deficiency (ID), known to affect over 1.2 billion individuals.

1.2.2. Clinical and diagnostic features.

Clinical features. Symptoms and signs may raise clinical suspicion of hypothyroidism during pregnancy (weight increase, sensitivity to cold, dry skin, *etc.*), but others may go unnoticed (asthenia, drowsiness, constipation, *etc.*). Because many women may remain asymptomatic, particular attention is required from obstetrical care providers for this condition to be diagnosed and to evaluate more systematically thyroid function when women attend the prenatal clinic for the first time. Only thyroid function tests confirm the diagnosis.

Diagnostic features. A serum TSH elevation suggests primary hypothyroidism, and serum free T_4 levels further distinguish between SCH and OH, depending on whether free T_4 is normal or clearly below normal for gestational age. Determination of thyroid autoantibodies titers—thyroid peroxidase (TPO) and thyroglobulin (TG) antibodies (TPO-Ab and TG-Ab)—confirms the autoimmune origin of the dis-

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Abbreviations: APLA, Antiphospholipid antibodies; ART, assisted reproductive technology; ATD, antithyroid drug; bw, body weight; DM, diabetes mellitus; FNAB, fine needle aspiration; FNAB, FNA biopsy; ID, iodine deficiency; IVF, *in vitro* fertilization; MMI, methimazole; OH, overt hypothyroidism; PPD, postpartum depression; PPT; postpartum thyroiditis; PTU, propylthiouracil; RAI, radioactive iodine; RNI, recommended nutrient intake; SCH, subclinical hypothyroidism; TAI, thyroid autoimmunity; TBG, T_4-binding globulin; TG, thyroglobulin; TG-Ab; TG antibody; TPO, thyroid peroxidase; TPO-Ab, TPO antibody; TRAb, TSH-R antibodies; TSAb, Thyroid-stimulating antibody; TSI, thyroid-stimulating immunoglobulins; TSH-R, TSH receptor; TV, thyroid volume; UIC, urinary iodine concentration; UIE, urinary iodine excretion; USI, universal salt iodinization.

order (6–8). The range of normal serum total T_4 is modified during pregnancy under the influence of a rapid increase in T_4-binding globulin (TBG) levels. Therefore, the nonpregnant total T_4 range (5–12 μg/dl or 50–150 nmol/liter) should be adapted in the second and third trimester by multiplying this range by 1.5-fold (9, 10). Reference ranges provided by the manufacturers of most free T_4 measurement kits have been established using pools of nonpregnant normal sera. Such reference ranges are not valid during pregnancy because free T_4 assays are influenced by serum changes (mainly in TBG and serum albumin). Authors have recently proposed to adapt serum free T_4 reference ranges to "laboratory-specific" or "trimester-specific" pregnancy ranges but, so far, no consensus has been reached on this issue (9–12). Therefore, we recommend caution in the interpretation of serum free T_4 levels during pregnancy and also that each laboratory should establish trimester-specific reference ranges for pregnant women.

Serum TSH values are influenced by the thyrotropic activity of elevated circulating human chorionic gonadotropin concentrations, particularly (but not only) near the end of the first trimester. Thus, by using the classical reference range for serum TSH (0.4 mIU/liter for the lower limit and 4.0 mIU/liter for the upper limit), one might misdiagnose as "normal" women who already have a slight TSH elevation and, conversely, one might suspect hyperthyroidism in normal women who have a blunted serum TSH value (13–14). Dashe *et al.* (14) have recently published a nomogram for serum TSH changes during pregnancy. They show that 28% of singleton pregnancies with a serum TSH greater than 2 SD scores above the mean would not have been identified by using the nonpregnant serum TSH range. Other authors have proposed to use "trimester-specific" reference ranges for serum TSH during pregnancy (12, 13). An example, illustrated in Fig. 1, shows that the lower normal limit of serum TSH is 0.03 mIU/liter in the first and second trimesters and is still reduced to 0.13 mIU/liter in the third trimester. Conversely, serum TSH levels above 2.3 mIU/liter (first trimester) and
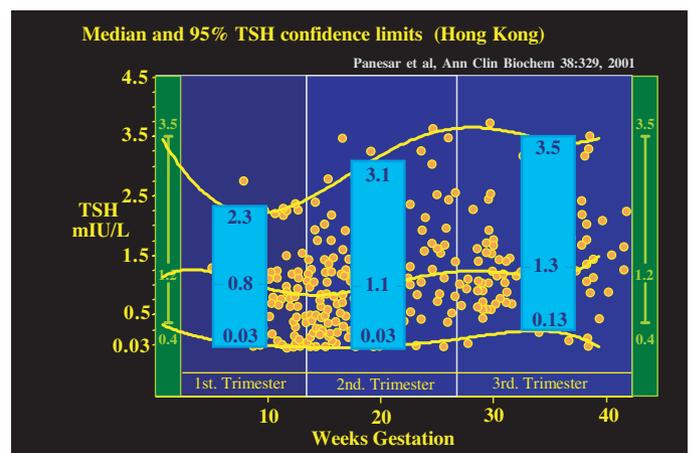

FIG. 1. Median and 95% confidence levels for TSH during pregnancy.

3.1–3.5 mIU/liter (second and third trimesters) may already be indicative of SCH.

1.3. EVIDENCE

1.3.1. Repercussions of hypothyroidism on pregnancy: maternal aspects. There is a known association between hypothyroidism and decreased fertility, although hypothyroidism does not preclude the possibility to conceive. In a study by Abalovich *et al.* (1), 34% of hypothyroid women became pregnant without treatment: 11% of them had OH and 89% SCH. When hypothyroid women become pregnant and maintain the pregnancy, they carry an increased risk for early and late obstetrical complications, such as increased prevalence of abortion, anemia, gestational hypertension, placental abruption, and postpartum hemorrhages. These complications are more frequent with OH than with SCH and, most importantly, adequate thyroxine treatment greatly decreases the risk of a poorer obstetrical outcome (1, 15–17).

1.3.2. Repercussions of hypothyroidism on pregnancy: fetal aspects. Untreated maternal OH is associated with adverse neonatal outcomes including premature birth, low birth weight, and neonatal respiratory distress. Increased prevalence of fetal and perinatal death has also been described, although it has not been confirmed in all studies. Obstetrical adverse effects such as gestational hypertension may also contribute to the overall increase in neonatal risks (1, 2, 15–18). Though less frequent than with OH, complications have also been described in newborns from mothers with SCH. Casey *et al.* (19) screened pregnant women before 20 wk gestation and reported a doubling of the rate of preterm delivery in those with SCH. Stagnaro-Green *et al.* (20) compared the thyroid status of women with preterm delivery to matched controls who delivered at term and showed that women with very preterm deliveries (before 32 wk) had a 3-fold increase in SCH. In a recent prospective randomized intervention trial by Negro *et al.* (21), the authors reported a significant decrease in the rate of preterm delivery among thyroid-antibody-positive women who had been treated with thyroxine, compared with thyroid-antibody-positive women who did not receive thyroxine administration and in whom thyroid function showed a gradual evolution toward SCH during gestation.

1.3.3. Maternal thyroid hormones and fetal brain development. A large body of evidence strongly suggests that thyroid hormone is an important factor contributing to normal fetal brain development (22–24). At early gestational stages, the presence of thyroid hormones in fetal structures can only be explained by transfer of maternal thyroid hormones to the fetal compartment, because fetal production of thyroid hormones does not become efficient until mid-gestation. Thyroid hormone and specific nuclear receptors are found in fetal brain at 8 wk after conception (25). Physiological amounts of free T_4 are found in the coelomic and amniotic fluids bathing the developing embryo in the first trimester (26). Studies of different cerebral areas in human fetuses indicated the presence of increasing concentrations of T_4 and T_3 by 11–18 wk after conception (27). The ontogenic patterns of thyroid hormone concentrations and the activity of iodo-

thyronine deiodinases show a complex interplay between the changing activities of the specific D2 and D3 iodothyronine deiodinases during gestation. This dual enzymatic system is interpreted to represent a regulatory pathway that fine-tunes the availability of T_3 required for normal brain development and avoids, at the same time, the presence of excessive amounts of T_3 (28–30).

1.3.4. Clinical studies on the role of maternal hypothyroidism for the psychoneurological outcome in the progeny. Because of the heterogeneity of what is commonly referred to as gestational "hypothyroidism," different clinical conditions must be considered. Thyroid insufficiency varies widely with regard to time of onset (first trimester *vs.* later), degree of severity (SCH *vs.* OH), progressive aggravation with gestation time (depending on the cause), and adequacy of treatment. To reconcile these variable clinical conditions into a global view of the repercussions of maternal hypothyroidism on the progeny is difficult. However, a common pattern clearly emerges. Overall, the results showed that there was a significantly increased risk of impairment in neuropsychological developmental indices, IQ scores, and school learning abilities in the offspring of hypothyroid mothers.

Three decades ago Evelyn Man and colleagues (31–33) published a series of articles suggesting that children born to mothers with inadequately treated hypothyroidism had significantly reduced IQs. However, the first large-scale prospective study on the outcome of children born to mothers with hypothyroidism during pregnancy was reported by Haddow *et al.* in 1999 (34). In this study, the severity of hypothyroidism varied from OH to probable SCH among the women whose children were investigated at school age. The main finding on extensive neuropsychological testing was that children born to untreated hypothyroid women had, on the average, an IQ score that was fully 7 points below the mean IQ of children born to healthy women and thyroxine-treated women. Furthermore, there were three times as many children with IQs that were 2 SD scores below the mean IQ of controls in the children born to untreated hypothyroid women. The study indicated that undisclosed and untreated hypothyroidism (and probable SCH) during pregnancy was associated with a risk of a poorer outcome in the progeny and a 3-fold increased predisposition for having learning disabilities.

Although still unpublished, a large set of data were reported at the 2004 annual meeting of the American Thyroid Association by Rovet *et al.* (35). The interest of this remarkable work is double. First, the authors investigated children born to women who had been treated for hypothyroidism during pregnancy, but in whom thyroxine administration was suboptimal (mean TSH between 5 and 7 mIU/liter). Second, the children were followed up and tested with extremely refined techniques up to 5 yr of age. Results were that some components of intelligence were affected, whereas others were not. At preschool age, the study-case children had a mild reduction in global intelligence that was inversely correlated with third trimester's maternal TSH. On the other hand, there was no negative impact on language, visual-spatial ability, fine motor performance, or preschool ability. The conclusion was that the offspring of women with sub-

optimally treated maternal hypothyroidism may be at risk for subtle and selective clinically relevant cognitive deficits, which depend specifically on severity and timing of inadequate maternal thyroid hormone availability.

A Dutch study investigated the developmental outcome in children born to women with early (first trimester) isolated low T_4 levels (*i.e.* a serum free $T_4 < 10.4$ pmol/liter, in the lowest 10th decile of "normal" pregnant T_4 values, with normal TSH) (36). Results suggested that early maternal low free T_4 was associated with a lower developmental index in the children at approximately 10 months of age. The same authors later published a second study based on similar selection criteria, but with a larger cohort and more refined motor and mental evaluations in infants aged 1 and 2 yr (37). Results were that 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. Of interest, infants of women with early low T_4, whose free T_4 level recovered spontaneously to normal later in gestation, had a normal development, suggesting that prolonged low T_4 was needed to impair fetal neuro-development.

Neural development in ID. The consequences of maternal hypothyroidism on the progeny must be considered separately because ID exposes both mother and fetus to thyroid underfunction (38). In a meta-analysis of 19 studies of infants' outcome in relation to ID, a significant downward shift of the frequency distribution of IQs was evidenced, with a mean 13.5 IQ points reduction in neuro-motor and cognitive functions (39). Because that meta-analysis encompassed conditions with more or less severe ID, the results cannot be fully extrapolated to mild-moderate ID. For this reason, the main results of seven studies (reported between 1989 and 1996) that have investigated the late outcome in children born to mothers with mild-moderate ID are summarized in Table 1 (40–46). Finally, a recent publication on the outcome of children born to mothers with ID during pregnancy, carried out in Sicily in an area with mild-moderate ID, indicated that the children had a greater than 10-point average deficit in global IQ. Furthermore, the study also pointed to attention deficit and hyperactivity disorder, which was found in 69% of the children born to mothers who had gestational hypothyroxinemia (47).

1.4. THERAPEUTIC ASPECTS

The administration of levothyroxine is the treatment of choice for maternal hypothyroidism, if the iodine nutrition status is adequate. Hypothyroid pregnant women require larger thyroxine replacement doses than do nonpregnant patients, and women who already take thyroxine before pregnancy usually need to increase their daily dosage by, on average, 30–50% above preconception dosage. Several reasons explain the incremented thyroid hormone requirements: the rapid rise in TBG levels resulting from the physiological rise in estrogen, the increased distribution volume of thyroid hormones (vascular, hepatic, fetal-placental unit), and finally the increased placental transport and metabolism of maternal T_4 (7, 48–50).

Thyroxine treatment should be initiated with a dose of 100–150 μg thyroxine/d or titrated according to body weight (bw). In nonpregnant women, the full replacement thyroxine dose is 1.7–2.0 μg/kg bw·d. During pregnancy, because of the increased requirements, the full replacement thyroxine dose should be increased to 2.0–2.4 μg/kg bw·d. In initially severe hypothyroidism, therapy may be initiated by giving for the first few days a thyroxine dose corresponding to two times the estimated final replacement daily dose, to rapidly normalize the extrathyroidal thyroxine pool (7, 51–53). In women who already receive thyroxine before conception, the need to adjust the preconception thyroxine daily dosage becomes manifest as early as by 4–6 wk gestation, hence justifying the adaptation of thyroxine replacement to ensure that maternal euthyroidism is maintained during early pregnancy. An alternative recommended by some thyroidologists is to anticipate the expected increase in serum TSH by raising the thyroxine dose before conception or as soon as pregnancy has been confirmed. It is important to note that 25% of hypothyroid women who are able to maintain a normal serum TSH level in the first trimester, and 35% of those who maintain a normal serum TSH level until the second trimester without increasing their daily dosage, will still require an increment in thyroxine replacement during late gestation to maintain a euthyroid status (7, 54, 55). The magnitude of thyroxine increment during pregnancy depends primarily on the etiology of hypothyroidism, namely the presence or absence of residual functional thyroid tissue.

TABLE 1. Neuropsychiatric and intellectual deficits in infants and schoolchildren born to mothers residing in conditions of mild to moderate ID

Region	Tests	Main findings	First author(s), date (Ref.)
Spain	Locally adapted: Bayley, McCarthy, Cattell	Lower psychomotor and mental development	Bleichrodt, 1989 (42)
Italy (Sicily)	Bender-Gestalt	Low perceptual integrative motor ability and neuromuscular and neurosensorial abnormalities	Vermiglio, 1990 (45)
Italy (Tuscany)	Wechsler Raven	Low verbal IQ, perception, and motor and attentive functions	Fenzi, 1990 (43)
Italy (Tuscany)	WISC reaction time	Lower velocity of motor response to visual stimuli	Vitti, 1992 (46), Aghini-Lombardi, 1995 (40)
India	Verbal, pictorial learning tests, tests of motivation	Lower learning capacity	Tiwari, 1996 (44)
Iran	Bender-Gestalt, Raven	Retardation in psychomotor development	Azizi, 1993 (41)

Table modified from Glinoer and Delange (38).

Women without residual functional thyroid tissue (after radioiodine ablation, total thyroidectomy, or due to congenital agenesis of the gland) require a greater increment in thyroxine dosage than women with Hashimoto's thyroiditis, who usually have some residual thyroid tissue. As a simple rule of thumb, the increment in thyroxine dose can be based on the initial degree of TSH elevation. For women with a serum TSH between 5–10 mIU/liter, the average increment in thyroxine dosage is 25–50 μg/d; for those with a serum TSH between 10 and 20 mIU/liter, 50–75 μg/d; and for those with a serum TSH greater than 20 mIU/liter, 75–100 μg/d.

Serum free T_4 and TSH levels should be measured within 1 month after the initiation of treatment. The overall aim is to achieve and maintain normal free T_4 and TSH at levels normal for pregnancy throughout gestation. Ideally, thyroxine treatment should be titrated to reach a serum TSH value less than 2.5 mIU/liter. As already alluded to, because it is sometimes difficult to correctly interpret the results of free T_4 and TSH measurements in the context of pregnancy, it is useful to optimize the monitoring of treatment during pregnancy by establishing laboratory-specific reference ranges for serum free T_4 and trimester-specific reference ranges for serum TSH. Once the thyroid function tests have been normalized by treatment, they should be monitored every 6–8 wk. If thyroid function tests remain abnormal, thyroxine dosage should be adjusted and tests repeated after 30 d, and so on until normalization of thyroid function tests. After parturition, most patients need to decrease thyroxine dosage received during pregnancy, over a period of approximately 4 wk postpartum. It should also be remembered that women with evidence of thyroid autoimmunity are at risk of developing postpartum thyroiditis (PPT), a syndrome that may justify differences in the pre- and post-pregnancy thyroxine requirements. It is therefore important to continue monitoring thyroid function tests for at least 6 months after delivery (7, 56).

In pregnant women in whom hypothyroidism has not been diagnosed until after the first trimester, there are indications that the offspring may suffer from impairment in final intellectual and cognitive abilities. The present consensus is to maintain the ongoing pregnancy, while rapidly normalizing maternal thyroid function by the administration of thyroxine. However, despite thyroxine treatment, it is impossible to fully reassure the future parents about potential brain damage that may have occurred if longstanding intrauterine severe hypothyroidism has been present.

1.5. RECOMMENDATIONS

1.5.1. Both maternal and fetal hypothyroidism are known to have serious adverse effects on the fetus. Therefore maternal hypothyroidism should be avoided. For OH, the USPSTF recommendation level is A; evidence is fair. Targeted case finding is recommended at the first prenatal visit. The USPSTF recommendation level is B; evidence is fair) (GRADE 2|⊕⊕○○) (1, 5, 34, 57).

1.5.2. If hypothyroidism has been diagnosed before pregnancy, we recommend adjustment of the preconception thyroxine dose to reach before pregnancy a TSH level not higher

than 2.5 mIU/liter. The USPSTF recommendation level is I; evidence is poor) (GRADE 2|⊕○○○) (9, 12, 13).

1.5.3. The thyroxine dose often needs to be incremented by 4–6 wk gestation and may require a 30–50% increment in dosage. The USPSTF recommendation level is A; evidence is good) (GRADE 1|⊕⊕⊕○.) (50, 51).

1.5.4. If OH is diagnosed during pregnancy, thyroid function tests should be normalized as rapidly as possible. Thyroxine dosage should be titrated to rapidly reach and thereafter maintain serum TSH concentrations of less than 2.5 mI/liter in the first trimester (or 3 mIU/liter in second and third trimesters) or to trimester-specific normal TSH ranges. Thyroid function tests should be remeasured within 30–40 d. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕) (10, 11, 13).

1.5.5. Women with thyroid autoimmunity (TAI) 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. The USPSTF recommendation level is A; evidence is fair) (GRADE 1|⊕⊕⊕○) (54, 57).

1.5.6. SCH (serum TSH concentration above the upper limit of the reference range with a normal free T_4) has been shown to be associated with an adverse outcome for both the mother and offspring. Thyroxine treatment has been shown to improve obstetrical outcome, but 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 thyroxine replacement in women with SCH. For obstetrical outcome, the USPSTF recommendation level is B; evidence is fair) (GRADE 1|⊕⊕○○); for neurological outcome, the USPSTF recommendation level is I; evidence is poor (○○○○) (1, 16, 19, 49).

1.5.7. After delivery, most hypothyroid women need to decrease the thyroxine dosage they received during pregnancy. The USPSTF recommendation level is A; evidence is good) (GRADE 1|⊕⊕⊕⊕) (56).

1.6. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, García A, Levalle O 2002 Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 12:63–68

The study concerns 150 pregnancies, corresponding to 114 women with primary hypothyroidism. Fifty-one pregnancies (34%) were conceived under hypothyroidism (16 with overt and 35 with SCH) and 99 pregnancies under euthyroidism with thyroxine therapy. When thyroxine treatment was not adequately adapted, a spontaneous miscarriage occurred in 60% of women with OH and 71% of women with SCH. Furthermore, premature delivery was observed in 20% of women with OH and 7% with SCH. Conversely, when thyroxine treatment was adequate and thyroid function remained normal, 100% of women with OH and 91% of women with SCH carried pregnancies to term and no abortion was observed in any of the groups. The authors concluded that

the outcome of pregnancy did not depend on whether hypothyroidism was initially overt or subclinical, but primarily on the adequacy of the thyroxine treatment.

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

Women with hypothyroidism who were planning pregnancy were observed prospectively before and throughout the pregnancies. Twenty pregnancies occurred in 19 women that resulted in 17 full-term births. An increase in the levothyroxine dose was necessary during 17 of 20 pregnancies. On the average, levothyroxine requirement increased by 47% during the first half of pregnancy. The median timing of this increase corresponded to a gestational age of 8 wk and a plateau was observed by wk 16. The increased thyroxine dose was required until delivery.

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

Prospective population study of 9,471 pregnant women in whom serum TSH was measured during the second trimester: hypothyroidism was diagnosed in 2.2% of them. Autoimmunity features corresponding to chronic thyroiditis were associated with thyroid dysfunction in 55% of women with SCH (serum TSH, 6–10 mU/liter) and more than 80% of women with OH (serum TSH, 11–200 mU/liter). Furthermore, the rate of fetal death was increased 4-fold (3.8% *vs.* 0.9%) in mothers with hypothyroidism compared with the control population with a normal serum TSH. The authors concluded that from the second trimester onward, the major adverse obstetrical outcome associated with raised TSH in the general population was an increased rate of fetal death. The authors also speculated that if thyroid replacement treatment avoided this problem, this would be another reason to consider population screening for thyroid dysfunction and autoimmunity.

Caixas A, Albareda M, Garcia-Patterson A, Rodriguez-Espinoza J, De Leiva A, Corcoy R 1999 Postpartum thyroiditis in women with hypothyroidism antedating pregnancy. J Clin Endocrinol Metab 84:4000–4005

Forty-one women (31 receiving levothyroxine replacement therapy and 10 receiving suppressive therapy for thyroid carcinoma were followed during the first year after delivery. A control group of 31 nonpregnant women with hypothyroidism (n = 21) or thyroid carcinoma (n = 10) were also followed during a similar period. A total of 23 of 41 (56%) had discordant requirements at follow up after delivery *vs.* only three of 31 in the control group (*P* < 0.001). The rate of patients with discordant prepregnancy *vs.* postpartum levothyroxine doses was higher in the noncarcinoma subgroup (68% *vs.* 20%; *P* < 0.01), whereas in the control group both subgroups displayed a similar rate of discordance. This study documents that women with hypothyroidism antedating pregnancy display changes in levo-

thyroxine requirements in the first year after delivery, suggesting the role of PPT.

Casey B, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, Cunningham FG 2005 Subclinical hypothyroidism and pregnancy outcomes. Obstet Gynecol 105:239–245

Serum TSH and free T_4 were measured in 25,756 women enrolled for prenatal care and who delivered a singleton infant (from November 2000 to April 2003). Among the cohort, a total of 17,298 (67%) women were enrolled at 20 wk gestation (or before), and the overall prevalence of SCH was 2.3%. In the women with SCH compared with the controls, pregnancy was 3-fold more likely to be complicated by placental abruption (relative risk, 3.0; 95% confidence interval, 1.1–8.2). Preterm birth, defined as a delivery at (or before) 34 wk gestation, was almost 2-fold more frequent in women with SCH (relative risk, 1.8; 95% confidence interval, 1.1–2.9).

Dashe JS, Casey BM, Wells CE, McIntire DD, Byrd EW, Leveno KJ, Cunningham FG 2005 Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. Obstet Gynecol 106:753–757

Serum TSH reference range evaluated in 13.599 singleton and 132 twin pregnancies, with individual values converted into a "nomogram" based on multiples of the median TSH at each week of pregnancy. Serum TSH decreased significantly during first trimester, with an even greater decrease (by 0.4 mIU/liter) in twin, compared with singleton pregnancies. Had a "classical" (nonpregnant, 0.4–4.0 mIU/liter) range been used rather than the nomogram, 28% of 342 singletons with TSH greater 2 SD scores above the mean would not have been identified. The upper TSH limit (97.5th percentile based on the nomogram) was approximately 3.0 to approximately 3.5 mIU/liter between wk 10 and 30. The TSH nadir was prolonged until late into the second trimester.

Demers LM, Spencer CA 2002 Laboratory support for the diagnosis and monitoring of thyroid disease. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines. Available at: http://www.nacb.org/lmpg/thyroid_lmpg_pub.stm

The authors consider that, until better data become available, the nonpregnant upper limit for serum TSH set at 2.5 mU/liter is also appropriate for the first trimester of pregnancy. Inasmuch as between-method biases for the measurement of serum TSH are minimal, there is no need for developing method-specific TSH ranges.

Glinoer D, Rihai 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

Prospective cohort study in Belgium of 1660 unselected consecutive pregnant women who underwent systematic screening for thyroid function and autoimmunity (TAI). Eighty-seven women were found to have positive thyroid antibodies with normal thyroid function tests (prevalence, 5.3%) in early pregnancy and were followed sequentially during gestation without treatment. Another group of 20

women, identified to have both positive antibodies and abnormal thyroid function tests (prevalence, 1.2%), were followed separately, because they required medical treatment. Thus, the overall prevalence of TAI in the cohort was 6.5%. In the group of women with TAI and normal thyroid function tests, main results were the following. In the first trimester, despite having TSH within the reference range limits, mean serum TSH was already significantly higher in TAI-positive women compared with controls. Furthermore, as gestation advanced to term, a significant fraction of these women progressively developed thyroid deficiency, with 40% of the women having a serum TSH above 3 mU/liter and 16% above 4 mU/liter at delivery. Finally, when comparing serum free T_4 levels between TAI-positive women and controls at delivery, it was found that, despite being euthyroid during early gestation, they were unable to maintain euthyroidism at the end of pregnancy, because at delivery their mean serum free T_4 was not only 30% below that of controls, but in addition their average serum free T_4 was at the lower limit of normality (10 pM/liter) and 42% of them were in the range of hypothyroid values. The conclusion was that women with asymptomatic TAI who are euthyroid in early pregnancy carry a significant risk of developing hypothyroidism progressively during gestation.

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

Sixty-two children (aged ~8 yr) were investigated prospectively and matched with 124 control children from the same schools, and all underwent extensive neuropsychological testing for IQ and school-learning abilities. The study children were born to mothers who had been identified retrospectively to have had hypothyroidism around mid-gestation, with elevated serum TSH and serum free T_4 levels that were on average 30% below the mean free T_4 of control mothers. Main results were that the full-scale IQ scores of children born to hypothyroid untreated mothers averaged 7 points lower than the mean IQ score of children born to control mothers ($P = 0.005$). Furthermore, three times as many children from mothers with untreated thyroid deficiency (19% *vs.* 5%) had IQ scores that were 2 SD scores below the mean IQ of the controls (that is <85). The conclusion was that undisclosed and hence untreated hypothyroidism occurring during the first half of pregnancy and presumably prolonged thereafter was associated with a risk of a poorer neuropsycho-intellectual outcome in the progeny and a 3-fold increased predisposition for having learning disabilities later in life.

Kaplan MM 1992 Monitoring thyroxine treatment during pregnancy. Thyroid 2:147–154

In this study, 65 hypothyroid pregnant women were subdivided into two groups. Group I consisted of 36 women with previous thyroid ablation (following radioiodine and/or surgical ablation). Group II consisted of 29 women with Hashimoto's thyroiditis. Those who were athyreotic required significantly greater increment of thyroxine re-

placement during pregnancy. In patients without residual thyroid tissue, thyroxine treatment increased from 114 ± 33 μg/d (corresponding to 1.75 μg/kg·d) before pregnancy to 166 ± 64 μg/d (corresponding to 2.25 μg/kg·d) during pregnancy, whereas in patients with Hashimoto's disease thyroxine dosage changed from 111 ± 25 μg/d (or 1.68 μg/kg·d) to 139 ± 52 μg/d (or 1.89 μg/kg·d) before and during pregnancy, respectively. These results indicate that women with Hashimoto's thyroiditis are likely to maintain a more suitable functional thyroid reserve, with the ability to compensate for the increased requirements in thyroid hormone associated with pregnancy.

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

Retrospective study of sera of 2000 pregnant women in Maine (U.S.) with the aim to determine the prevalence of undisclosed gestational hypothyroidism. Results showed that 49 women had a serum TSH value above 6 mU/liter at 15–18 wk gestation, corresponding to an overall 2.5% prevalence of hypothyroidism. Among these women, the majority (43 of 49) presented SCH, with 55% of them having positive thyroid autoantibodies (compared with 11% in the controls). Hitherto undiagnosed overt thyroid deficiency was present in six of 49 of the women and in this more severely affected subgroup the frequency of positive thyroid autoantibodies reached 90%.

Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH 1993 Perinatal outcome in hypothyroid patients. Obstet Gynecol 81:349–353

The study concerns the perinatal outcome in 68 hypothyroid patients, 23 with OH and 45 with SCH. Gestational hypertension (namely eclampsia, preeclampsia, and pregnancy-induced hypertension) was significantly more common in women with OH (22%) and SCH (15%) than in the control population (8%). In addition, 36% of the overt and 25% of the subclinical hypothyroid patients who had remained hypothyroid until delivery developed gestational hypertension. The low birth weights observed in both women with OH and SCH was secondary to premature delivery due to gestational hypertension. The authors concluded that normalization of thyroid function tests may prevent gestational hypertension and its consequent complications in hypothyroid pregnant women.

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

The authors analyzed retrospectively thyroid function in 12 pregnant women who received thyroxine treatment for primary hypothyroidism. Because of elevated serum TSH levels, the thyroxine dosage had to be increased in nine of 12 patients. The mean thyroxine dosage was 100 μg/d before pregnancy and was increased to 150 μg/d during pregnancy ($P < 0.01$). Among the three patients who did not require an increase in thyroxine dosage, two had a low serum TSH before pregnancy, suggesting excessive replacement. During postpartum, the mean thyroxine dose was decreased to 117

μg/d ($P < 0.01$, compared with pregnancy dosage). These results indicate the need to increase the thyroxine dosage in the majority of with primary hypothyroidism during pregnancy.

Panesar NS, Li CY, Rogers MS 2001 Reference intervals for thyroid hormones in pregnant Chinese women. Ann Clin Biochem 38:329–332

To establish gestation-related reference intervals for thyroid hormones in a Chinese population, the authors prospectively studied 343 healthy pregnant women and 63 nonpregnant controls. TSH, free T_4, and free T_3 were measured and the median, 2.5th and 97.5th percentiles at 4-wk intervals were calculated. Free T_3 decreased during pregnancy, whereas free T_4 initially increased, peaking between 9 and 13 wk and then decreased. TSH mirrored changes in free T_4. The authors concluded that the gestation-related reference intervals for thyroid hormones should alleviate the misinterpretation of thyroid function in pregnancy.

Pop V, Brouwers EP, Vader HL, Vulsma T, Van Baar AL, De Vijlder JJ 2003 Maternal hypothyroxineaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 59:282–288

Prospective follow-up study of pregnant women and their infants up to the age of 2 yr. The women were selected to have isolated hypothyroxinaemia during early pregnancy, with a serum free T_4 below the lowest tenth percentile of control pregnant women but with a normal serum TSH. Main results were that the infants born to mothers with hypothyroxineaemia at 12 wk gestation (n = 63) had delayed mental and motor function both at the ages of 1 and 2 yr compared with control infants (n = 62), assessed by the means of the Bailey Scales of Infant Development. The study also showed that infants born to mothers with hypothyroxinemia in the first trimester but who spontaneously recovered normal free T_4 levels during later gestation (at 24 and 32 wk) had a normal development, thus indicating that early hypothyroxineaemia alone, when it was not prolonged during later gestational stages, did not adversely affect the infants' motor and mental development.

Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ 2004 Trimester-specific changes in maternal thyroid hormone, TSH and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. Thyroid 14:1084–1090

The authors describe the interrelationships of thyroid tests based on trimester-specific concentrations in healthy, iodine-sufficient pregnant women across trimesters and postpartum. Trimester-specific total T_3, free T_4, TSH, and TG concentrations were significantly different between first and third trimesters (all $P < 0.05$). Second and third trimester values were not significantly different for free T_4, TSH and TG, although total T_3 was significantly higher in the third, relative to the second trimester. Total T_4 was not significantly different at any trimester. These results show that in iodine sufficient women serum total T_3, free T_4, TSH, and TG tend to change throughout the course of pregnancy, whereas total T_4 after the first trimester does not.

SECTION 2. MANAGEMENT OF HYPERTHYROIDISM: MATERNAL AND FETAL ASPECTS

2.2. BACKGROUND

2.2.1 Maternal hyperthyroidism. The prevalence of hyperthyroidism in the United States is approximately 1% (0.4% clinical and 0.6% subclinical) according to the NHANES survey (58). The most common cause of hyperthyroidism is Graves' disease, which is 5- to 10-fold more common in women, with a peak incidence during the reproductive age. Thus, hyperthyroidism in pregnancy is not rare and its reported prevalence ranges from 0.1% to 0.4%, with Graves' disease accounting for 85% of cases (59–61). Single toxic adenoma, multinodular toxic goiter, and thyroiditis comprise most of the remaining cases during pregnancy, whereas significant gestational thyrotoxicosis, factitious thyrotoxicosis, and hydatidiform molar disease are uncommon (62).

As in other autoimmune diseases, the activity level of Graves' disease may fluctuate during gestation, with exacerbation during the first trimester and gradual improvement during the later half. Patients with Graves' disease may also experience an exacerbation shortly after delivery (63). Rarely, labor, cesarean section, and infections may aggravate hyperthyroidism and even trigger a thyroid storm (64–66).

Autoimmune thyroiditis occurs in up to 10% of women in the reproductive age (67). Generally, the result is hypothyroidism, although a hyperthyroid phase of Hashimoto's thyroiditis and silent thyroiditis may both occur. PPT occurs after up to 10% of all pregnancies and may have a hyperthyroid phase, usually within the first month or two (68). Because PPT may begin between 6 wk to 6 months after delivery, and occasionally as long as 1 yr later, it is not uncommon to find women who have started on their next pregnancy within this time frame. Furthermore, "postpartum" thyroiditis may be triggered by a miscarriage occurring as early as 6 wk gestation and such women often conceive again within a few months (69). Because the hyperthyroid phase of thyroiditis is often followed by a hypothyroid phase, and because hypothyroidism is an important risk for fetal development, careful sequential monitoring is necessary to detect and treat the hypothyroid phase of this illness.

Patients with gestational thyrotoxicosis present in the mid to late first trimester, often with hyperemesis. Usually classic hyperthyroid symptoms are absent or minimal, except for weight loss, which may be a result of vomiting and poor nutrition (70, 71). Graves' disease must be differentiated from gestation thyrotoxicosis so that a decision about ATD therapy can be reached. (See *Gestational Hyperemesis and Hyperthyroidism*, Section 3.)

2.2.2. Fetal thyroid function. The fetal thyroid begins concentrating iodine at 10–12 wk gestation and is under control of fetal pituitary TSH by approximately 20 wk gestation. Fetal serum levels of TSH, TBG, free T_4, and free T_3 increase throughout gestation, reaching mean adult levels at approximately 36 wk (72). TSH does not cross the placenta. However, clinically significant amounts of maternal T_4 do cross the placenta. In neonates with congenital hypothyroidism, enough maternal thyroid hormone crosses the placenta to

prevent stigmata of hypothyroidism at birth and to maintain cord blood thyroid hormone levels at near 50% of normal (73). In addition, TSH-releasing hormone (TRH), iodine, TSH receptor (TSH-R) antibodies, and antithyroid drugs (ATDs) cross the placenta readily.

Fetal and neonatal risks of maternal hyperthyroid disease are related to the disease itself and/or to the medical treatment of the disease. Inadequately treated maternal thyrotoxicosis is associated with an increased risk of medically indicated preterm delivery, intrauterine growth restriction and low birth weight, preeclampsia, congestive heart failure, and intrauterine death (74, 75). In addition, overtreatment of the mother with thioamides can result in iatrogenic fetal hypothyroidism (76).

2.3. EVIDENCE

2.3.1. Diagnosis of maternal hyperthyroidism. Because nonspecific symptoms of hyperthyroidism such as tachycardia, warm moist skin, tremor, and systolic murmur may be mimicked by normal pregnancy, the presence of classic thyroid ophthalmopathy, a significant goiter, or pretibial myxedema (while rare) may point to a diagnosis of true Graves' disease. A careful physical examination should be performed in all patients.

Patients suspected of having hyperthyroidism require measurement of serum TSH, T_4, T_3 levels, and thyroid receptor antibodies. However, interpretation of thyroid function tests must be made in relation to the hCG-mediated decrease in serum TSH levels and the increase in TBG concentrations that occur during pregnancy (77–79). In the normal pregnant woman, TSH levels typically fall in the mid to late first trimester coincident with rising hCG levels. The median serum TSH level in the first half of pregnancy is approximately 0.8 μU/ml, with 95% confidence interval lower limit of 0.03 μU/ml (13). Therefore, subnormal serum TSH levels in the first half of pregnancy should not be interpreted as diagnostic of hyperthyroidism (see Fig. 1, *Section 1.2.2*).

Free hormone measurements by one- or two-step analog methods may perform differently during pregnancy because of the known alterations in two thyroid hormone binding proteins, increased serum TBG levels, and decreased serum albumin concentrations (11–13, 79, 80). Measurement of free T_4 hormone concentration by equilibrium dialysis is costly and not universally available. However, it appears that serum free T_4 levels measured by both equilibrium dialysis and automated methodologies are increased over nonpregnant reference ranges in the first trimester and then decrease so that by the third trimester, the 95% confidence interval for serum free T_4 concentration may be 30% lower than the nonpregnant reference range (11, 80). For practical purposes, keeping the free T_4 in the upper nonpregnant normal range is appropriate. Alternatively, because the changes in total T_4 levels during gestation are predictable, the nonpregnant reference limits just need to be adjusted by a factor of 1.5 to determine the normal range for pregnancy (81).

Up to 60% of women with hyperemesis gravidarum have a subnormal TSH and nearly 50% have an elevated free T_4 concentration (70). (See *Gestational Hyperemesis and Hyper-*

thyroidism, Section 3.) In situations where doubt exists, measurement of serum total T_3 concentration and T_3 resin uptake may be helpful, as only 12% of women with hyperemesis gravidarum have an elevated free T_3 index (70).

Most patients with Graves' disease will have detectable TSH-R antibodies (TRAb) (12). Measurement of TRAb may also help to distinguish Graves' disease from gestational thyrotoxicosis in the first trimester as TRAb are negative in gestational hyperthyroidism. Because Graves' disease tends to undergo immunological remission after the late second trimester (63), detection of TRAb may depend upon gestational age at measurement.

2.3.2. Diagnosis of fetal hyperthyroidism. Although fetal hyperthyroidism requiring treatment is rare (under 0.01% of pregnancies), it should be considered possible in any woman with a past or current history of Graves' disease. The likelihood of developing fetal hyperthyroidism requiring treatment is related to the level of maternal stimulating TRAb levels, medical treatment of maternal disease, and patient history. Fetal hyperthyroidism can be associated with growth restriction, fetal tachycardia, fetal goiter, fetal hydrops, preterm delivery, and fetal death (82–86). The diagnosis is suggested by fetal tachycardia, intrauterine growth restriction, fetal goiter, fetal cardiac failure, or fetal hydrops. Treatment may be given on the presumptive diagnosis, but definitive diagnosis (if needed) requires umbilical cord blood sampling for fetal thyroid function and carries a significant risk to the fetus (87–90). Depending on the gestational age at presentation, umbilical cord blood sampling in a fetus of a mother with Graves' disease with the above signs or symptoms may be warranted if the diagnosis cannot be adequately inferred on clinical grounds and if the information would change management.

Symptomatic neonatal hyperthyroidism should be considered an emergency and treated appropriately. Neonatal hyperthyroidism is typically due to transplacental passage of maternal TRAb, but activating mutations of TSH-R or of G proteins, and *de novo* Graves' disease in the neonate, should be considered in the differential diagnosis (91–93).

2.3.4. Adverse effects of maternal hyperthyroidism: pregnancy outcome. Lack of control of hyperthyroidism is associated with adverse pregnancy outcomes (62). The risk of complications for both mother and fetus is related to the duration and control of maternal hyperthyroidism. The highest incidence of complications occurred in women with the poorest control and the lowest incidence in those with adequate treatment (62, 74, 75). Inadequately treated maternal thyrotoxicosis is associated with an increased risk of medically indicated preterm delivery. In one study 88% of the untreated, compared with 25% of the partially treated and 8% of the adequately treated mothers, had a medically indicated preterm delivery (75). In addition, untreated women are twice as likely to develop preeclampsia during pregnancy as are women receiving ATDs (75). In retrospective studies of almost 450 patients (62, 74, 75), the rates of several complications in treated *vs.* untreated patients were as follows: preeclampsia, 7% *vs.* 14–22%; congestive heart failure, 3% *vs.* 60%; and thyroid storm, 2% *vs.* 21%. Even in those hyperthyroid

women in whom control was achieved by delivery, the incidences of preeclampsia (11.1%) and preterm delivery (8.4%) were elevated above control (75).

Multiple retrospective studies have reported an association of poorly controlled hyperthyroidism with intrauterine growth restriction or low birth weight and possibly fetal loss as compared with treated euthyroid women (74, 75). Mean low birth weight and number of stillbirths appeared to be related to the severity of thyrotoxicosis, with four of eight women with untreated thyrotoxicosis having stillbirths (74). The prevalence of low birth weight, defined as less than 2500 g at term, was evaluated in hyperthyroid patients (n = 35) *vs.* euthyroid women (n = 153), of whom 54 were euthyroid throughout the pregnancy and 99 had euthyroidism established by the third trimester. Corrections were made for the confounders of preterm delivery and preeclampsia. The prevalence of low birth weight in the hyperthyroid group was 22.9% *vs.* 9.8% in the euthyroid group, which in turn was consistent with the uncomplicated control group (9.7%). Hyperthyroidism in the third trimester was an independent risk factor for low birth weight (odds ratio, 4.1; 95% confidence interval, 1.09–15.0) (94). Finally, there are limited data that untreated maternal hyperthyroidism is associated with miscarriage (95, 96). A recent study showed that women with a genetic resistance to thyroid hormone, who were euthyroid but had elevated T_4, experienced a significantly increased miscarriage rate compared with unaffected couples (97). The hypothesis was that the elevated maternal thyroid hormone levels cause hyperthyroidism in the fetuses not carrying the mutated gene for thyroid hormone resistance.

2.3.5. Adverse effects of maternal hyperthyroidism: fetal and neonatal thyroid dysfunction. Because a large proportion of thyroid dysfunction in women is mediated by antibodies that can cross the placenta (Graves' disease and chronic autoimmune thyroiditis), there is legitimate concern for risk of immune-mediated hypothyroidism or hyperthyroidism in the neonate. Women with Graves' disease have TRAbs that can stimulate or inhibit the fetal thyroid. Inhibitory TRAbs may cause transient neonatal hypothyroidism in neonates of mothers with Graves' disease (98, 99).

Because the antireceptor antibodies may have a mixture of three different actions on the TSH-R, are given different names, and are assayed by several procedures, there is ample room for confusion. All antibodies that can compete with TSH for binding to the TSH-R are identified as TSH-binding inhibitory immunoglobulins. These antibodies are measured using commercially available kits that record the percentage of inhibition of TSH binding to a membrane preparation of TSH-Rs. The assay does not measure the ability of the antibody to stimulate the receptor, but binding and stimulation frequently go in parallel. Therefore this assay is often used as a surrogate for an assay of receptor stimulating antibodies. Antibodies that stimulate the receptor (*i.e.* thyroid stimulating antibodies) are measured by their ability to stimulate cAMP production in a preparation of cell membranes containing the TSH-R. This assay is specific for the pathogenic antibody in Graves' disease but is not generally available in hospital or commercial laboratories. The final set of antibodies are those that bind to the receptor and inhibit the stim-

ulating activity of TSH. These antibodies may be clinically significant because they can cause hypothyroidism (including in the fetus), but they are usually measured only in a research setting. Their assay depends upon their ability to reduce cAMP production induced by TSH, in the setting of the thyroid-stimulating antibody (TSAb) assay described above.

One to five percent of neonates of mothers with Graves' disease have hyperthyroidism or neonatal Graves' due to the transplacental passage of stimulating maternal TRAb (96). The incidence is low because of the balance of stimulatory and inhibitory antibodies and thioamide treatment of the mothers (100). Maternal antibodies are cleared less rapidly than thioamides in the neonate, sometimes resulting in delayed presentation of neonatal Graves' disease (100). The incidence of neonatal Graves' disease is not directly related to maternal thyroid function. Women who have been treated surgically or with 131-I before pregnancy and require no thioamide treatment are at higher risk for neonatal Graves' disease, due to the lack of the suppressive thioamide and the potential persistence of TRAb (100).

Risk factors for neonatal thyroid dysfunction include history of a previously affected baby, prior ablative treatment with 131-I, and elevated maternal TRAb at time of delivery (82, 83, 100, 101). Incidence of neonatal thyroid dysfunction was 67% if TRAbs were greater than 130% (response given as % of normal control value, and <115% is considered normal) and 83% if greater than 150%, compared with 11% with less than 130% antibody response (101). In this study, neonatal thyroid dysfunction included overt thyrotoxicosis, chemical thyrotoxicosis, transient hypothyroidism, and central hypothyroidism, and only 2.6% of the neonates had overt thyrotoxicosis requiring treatment (101). In a recent study that defined normal as less than 1.3 index units (IU) or less than 130%, a TRAb threshold of greater than 5 IU had a sensitivity of 100% and specificity of 76% for neonatal thyrotoxicosis (83).

The risk of fetal thyroid dysfunction was evaluated in a report that followed 26 fetuses (18 women) with Graves' disease over 10 yr (82). Nine women agreed to umbilical cord blood sampling and two fetuses (8%) with hyperthyroidism were found. Both of these fetuses were born to mothers who were treated with 131-I before pregnancy and had high TSAb (>249%). None of the other 21 neonates had any thyroid disease requiring treatment after delivery. In other studies umbilical blood sampling also confirmed fetal hyperthyroidism in fetuses with signs of thyrotoxicosis including tachycardia, fetal goiter, or intrauterine growth restriction (84, 85, 90). Fetal goiter, associated with treatment of Graves' disease with thioamides, can be due to either fetal hypothyroidism from maternal ATD treatment or fetal hyperthyroidism from maternal antibody transfer (76, 102). Umbilical cord blood sampling carries a risk of fetal loss of 1–2% (103, 104). These data indicate that the highest risk factors for significant fetal and neonatal thyroid disease include fetal signs (tachycardia, intrauterine growth retardation, fetal cardiac failure, fetal goiter), maternal history of a prior affected baby or prior treatment with 131-I, and an elevated maternal TSAb.

Luton *et al.* (102) followed 72 mothers with past or present Graves' disease by clinical evaluation, TRAb assays, and

ultrasound evaluation of fetal thyroid and bone age. In 31 pregnancies with negative maternal TRAb assay and no ATD treatment, all infants were normal at birth. Of the remaining 41 pregnancies, 30 were associated with positive TRAb or ATD treatment but had normal fetal thyroid ultrasonography at 32 wk and no clinical evidence of thyroid dysfunction. All but one was normal at birth. Of 11 fetuses that had a goiter, seven were hypothyroid and four were hyperthyroid. The diagnosis of fetal hyperthyroidism was associated with high maternal TRAb, accelerated bone maturation, and fetal goiter. Fetal hypothyroidism was associated with low TRAb levels, high doses of maternal ATD treatment, maternal T_4 in the low normal range, delayed bone maturation, and fetal goiter. These authors recommend TRAb assay in women with current or past Graves' disease at the beginning of pregnancy or with other screening procedures at the end of the first trimester, and close observation of pregnancies with elevated TRAb levels or ATD treatment by monthly fetal ultrasonography after 20 wk. In their study, women with negative TRAb and on no antithyroid medication were not at risk for fetal goiter or thyroid disease.

2.3.6. Therapy of maternal hyperthyroidism. ATDs are the main treatment for Graves' disease during pregnancy. Propylthiouracil (PTU) and methimazole (MMI, Tapazole) and carbimazole have been used during gestation. They inhibit thyroid hormone synthesis via reduction in iodine organification and iodotyrosine coupling. Pregnancy itself does not appear to alter the maternal pharmacokinetics of MMI, although serum PTU levels may be lower in the latter part of gestation than in the first and second trimesters (105). PTU is more extensively bound to albumin at physiological pH, whereas MMI is less bound, which hypothetically might result in increased transplacental passage of MMI relative to PTU. A recommendation for the preferred use of PTU during pregnancy is in part based on a single report of reduced transplacental passage of PTU as compared with MMI. However, in this study, only six women without a history of thyroid disease received a single injection of either [^{35}S]MMI or [^{35}S]PTU before undergoing a therapeutic abortion in the first half of pregnancy (106). A more recent study measuring serum PTU levels in hyperthyroid mothers treated with PTU until term found that the cord PTU concentration was higher than maternal levels (107). No such data evaluating simultaneous maternal and cord levels are available for MMI. Furthermore, a perfusion study conducted on placental tissue from women without thyroid disease, who underwent cesarean section at term, revealed similar placental transfer kinetics for both PTU and MMI (108). Therefore, differential placental transfer of PTU and MMI appears unlikely, and by itself does not support the preferential use of PTU *vs.* MMI. Finally, the effect on fetal/neonatal thyroid function appears to be similar for the two agents. In 77 newborns of mothers who were euthyroid while being treated with either PTU or MMI, there were no differences between the PTU- and the MMI-treated newborns in thyroid function measured in cord blood at birth (109). (See also the discussion below.)

Subclinical hyperthyroidism (TSH below normal limits with free T_4 and total T_4 in the normal pregnancy range, and unaccompanied by specific clinical evidence of hyperthy-

roidism) is seen in hyperemesis gravidarum syndrome. Treatment of maternal subclinical hyperthyroidism has not been found to improve pregnancy outcome and may risk unnecessary exposure of the fetus to ATDs (70, 71, 110, 111).

2.3.7. Maternal ATD therapy: effects on the fetal thyroid. ATD treatment of pregnant women must be aimed to restore normal maternal thyroid function while ensuring that fetal thyroid function is minimally affected. There are seven published studies examining a dose response relationship between maternal ATD dose and neonatal thyroid function. Three have reported a direct correlation (101, 108, 112), and four have reported no correlation (107, 109, 111, 113). In fact, one study reported that even low daily ATD dosages (PTU 100 mg or less, MMI 10 mg or less) at term might affect fetal thyroid function. An elevated cord TSH level was found in 23% of babies born to such PTU-treated mothers and in 14% of those born to mothers treated with MMI (109). The lack of correlation between maternal dosage and fetal thyroid function may also reflect maternal factors as well, because there is individual variability in serum PTU levels after a standard oral dose (114) as well as in the transplacental passage of maternal TRAbs that stimulate the fetal thyroid.

Given these varied influences on fetal thyroid function, coupled with individual maternal differences in ATD pharmacology, it is not surprising that fetal thyroid status is not strictly correlated with maternal ATD dosage. The literature indicates that current maternal thyroid status rather than ATD dose may be the most reliable marker for titration of ATD therapy to avoid fetal hypothyroidism (108, 114). If the maternal serum free T_4 concentration is either elevated or maintained in the upper third of the normal nonpregnant reference range, serum free T_4 levels are normal in more than 90% of neonates. However, if the maternal serum free T_4 is in the lower two thirds of the normal nonpregnant reference range, 36% of neonates have a decreased free T_4. A decreased free T_4 is found in all neonates if the maternal free T_4 is below normal (111).

2.3.8. Maternal ATD therapy: teratogenicity. There have been reports of two distinct teratogenic patterns associated with MMI: aplasia cutis and choanal/esophageal atresia. The data supporting these associations are controversial. Aplasia cutis occurs at a baseline rate of 1 in 33,000 births, and in one report the rate associated with MMI was not different from this baseline rate (115). In another series no cases of aplasia cutis were reported from a group of 243 MMI-treated women (116). However, multiple case reports associating aplasia cutis with MMI exposure have been published, and an increased rate of aplasia cutis was noted in Spain in an area where MMI was used in animal feed (60, 117).

Case reports have suggested that choanal or esophageal atresia, which is a more severe anomaly requiring major surgery to repair, was associated with MMI use (118, 119). In contrast, in a prospective cohort study, comparing MMI-exposed infants to controls not exposed to MMI, there was no significant difference in incidence of major anomalies or spontaneous abortions (120). The MMI exposure occurred in the first trimester of pregnancy. The authors found two cases of either choanal or esophageal atresia among the 241 MMI-

exposed infants, but no such cases were found in the control group. They concluded that choanal and esophageal atresia may have a higher incidence than expected in fetuses exposed to first trimester MMI. Although the data are not conclusive for an association between MMI exposure and aplasia cutis or choanal/esophageal atresia, there are no data to support an association between congenital anomalies and PTU. It should be noted that MMI and its progenitor carbimazole are the only medications available in many countries, and therefore these drugs must be employed despite the potential complications cited. However, where available, PTU is preferred as the initial therapy for maternal hyperthyroidism.

Aside from potential induction of hypothyroidism, and the noted possible teratogenic effects, there are no other long-term pediatric or adult effects reported to be associated with either PTU or MMI in *in utero* exposure. An evaluation of 15 MMI- and 16 PTU-exposed individuals at 4–23 yr of age found no differences in IQ or in verbal or performance skills compared with unexposed siblings (121). In addition no difference was found in mental or psychomotor development in 12 MMI-exposed children at 7 yr of age, compared with similar aged children of euthyroid mothers with Graves' disease not treated with antithyroid medication during pregnancy (122). A more recent study (123) also found no difference in the Wechsler IQ scores of children born to MMI-treated (up to 20 mg MMI daily) hyperthyroid mothers during pregnancy and those born to euthyroid women.

2.3.9. Maternal ATD therapy: lactation. Historically, many texts have advised against breast-feeding in women treated with ATDs because of the presumption that the ATD was present in breast milk in concentrations sufficient to affect the infant's thyroid. However, four recent studies reported no alteration in thyroid function in a total of 159 newborns breast-fed by mothers treated with daily doses of PTU (50–300 mg), MMI (5–20 mg), or carbimazole (5–15 mg) for periods ranging from 3 wk to 8 months (124–128). Even in women who were overtreated and developed elevated serum TSH levels, the babies' thyroid function tests remained normal. Therefore, ATD therapy (PTU <300 mg/d, MMI <20 mg/d) may be considered during lactation, although the number of reported infants is small. The drug should be taken by the mother after a feeding. Until more studies are available, monitoring the infant's thyroid function may be considered. In addition, the theoretical possibility of the infant's developing ATD side effects via ATD ingestion through lactation has not been reported.

2.3.10. Propranolol. Propranolol may be used to treat symptoms of acute hyperthyroid disease and for preoperative prearation, and there are no significant teratogenic effects of propranolol reported in humans or in animals (129). Use of propranolol in late pregnancy has been associated with mild and transitory neonatal hypoglycemia, apnea, and bradycardia (129). If a neonate develops any of these effects, they generally resolve within 48 h. Finally, there are case reports suggesting an association between propranolol use and intrauterine growth restriction, but this remains controversial (129, 130). If a patient requires long-term propranolol treat-ment, careful monitoring of fetal growth is advised. Propranolol is approved by The American Academy of Pediatrics for breast-feeding women. It should be noted that all beta blockers are listed by the FDA as either pregnancy category B or C.

2.3.11. Iodides. Chronic use of iodides during pregnancy has been associated with hypothyroidism and goiter in neonates, sometimes resulting in asphyxiation because of tracheal obstruction (105, 131). However, a recent report of low-dose potassium iodide (6–40 mg/d) administered to selected pregnant hyperthyroid women, with maintenance of maternal free T_4 levels in the upper half of the normal range, did not cause goiter, although 6% of newborns had an elevated serum TSH level (132). Because the experience with iodides is more limited, iodides should not be used as a first-line therapy for women with Graves' disease, but they could be used transiently if needed in preparation for thyroidectomy.

2.3.12. 131-I. Radioactive iodine (RAI) diagnostic tests and therapy are contraindicated during pregnancy, and all women who could potentially become pregnant should have a pregnancy test before 131-I administration. The fetus is exposed to the radiation from the 131-I circulating in the mother's blood, which is approximately 0.5–1.0 rad (5–10 mGy) per mCi administered. Because fetal thyroid uptake of RAI commences after 12 wk, exposure to maternal 131-I before the 12th week of pregnancy is not associated with fetal thyroid dysfunction (133). However, treatment after 12 wk leads to significant radiation to the fetal thyroid. Multiple instances of exposure causing fetal thyroid destruction and hypothyroidism have been reported, and as well instances in which possible neural damage has ensued because the fetus was left untreated (133–135).

It is considered routine to question women who are potentially fertile about possible pregnancy before administration of any radioisotope, and blood samples for determination of β-hCG are routinely taken. However, there is an approximate 1-wk interval after fertilization before this test becomes positive, so in addition some therapists suggest abstinence be documented for this interval. It has also been suggested that pregnancy be avoided for 4 months after RAI treatment of males to ensure that one cycle of spermatogenesis has occurred (136). In addition, 131-I is contraindicated in breast-feeding mothers, and breast-feeding should cease if the exposure is unavoidable.

Inadvertent treatment nevertheless may occur, raising the question of what information should be given to the mother. This inadvertent exposure is most likely in the first trimester, the crucial period of organogenesis, when the patient does not yet realize she is pregnant. Fetal radiation related to treatment of hyperthyroidism may expose the fetus to 5–10 rads or more (133). Fetal exposure to high doses of radiation before organogenesis (before 4–6 wk gestation) can lead to miscarriage or have no effect. Radiation exposure later in gestation can be associated with malformations, growth restriction, developmental delay and induction of malignancies (137). However, the likelihood of these effects is not certain. In one study of inadvertent treatment with 131-I in the first trimester, only 3% of exposed fetuses were hypo-

thyroid, 2% developed mental deficiency (presumably related to hypothyroidism), and 1% of the women had spontaneous abortions (138). Exposure after 12 wk can induce thyroid ablation, requiring intrauterine thyroid hormone replacement and lifelong therapy for hypothyroidism.

2.3.13. Surgery. Subtotal thyroidectomy is only considered during pregnancy as therapy for maternal Graves' disease if a serious adverse reaction to ATD therapy occurs, if persistently high doses of ATD are required to control maternal hyperthyroidism, or if a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. There are no data to support an absolute upper cutoff ATD dosage above which thyroidectomy must be performed. If a woman has experienced severe ATD-related side effects such as agranulocytosis, she should receive transient therapy with potassium iodide solution (50–100 mg/d) for 10–14 d before surgery. This therapy is recommended to reduce vascularity of the thyroid gland and is believed safe during this period of exposure. Propranolol can also be administered preoperatively.

2.3.14. Surgery: fetal aspects associated with preparation for and conduct of thyroid surgery. There are few data that specifically address problems associated with thyroid surgery in pregnancy, or that compare the outcome in patients treated medically *vs.* those treated by surgery (139). Because surgery carries more risks in general than medical therapy, contemporary advice routinely favors an initial medical approach. However, as with other nonobstetric surgery in pregnancy, certainly it is being performed when deemed to be medically necessary for the mother's health (140). All of these decisions should be undertaken with a multidisciplinary group including representation from endocrinology, surgery, perinatology, and anesthesiology.

Surgery is deemed safest in pregnancy if it can be undertaken in the second trimester when organogenesis is complete, and thus the fetus is at minimal risk for teratogenic effects of medications, and the uterus is relatively resistant to contraction-stimulating events. In addition, after 12 wk the likelihood that any patient will have a spontaneous miscarriage is reduced. Of note, no anesthetic drug has been proven to be teratogenic in the human. The reader is referred to an excellent review of the anesthetic principles of nonobstetric surgery in pregnancy (141). Important general considerations for the pregnant surgical patient include positioning in left lateral tilt to maximize uterine blood flow. If the surgery occurs after viability, fetal cardiac monitoring is appropriate.

2.3.15. Therapy of fetal hyperthyroidism or fetal hypothyroidism associated with maternal antithyroid treatment for Graves' disease. Case reports have described various treatments of fetal hyperthyroid and hypothyroid disease (76, 84, 85, 90). These include treatment of a fetus with a goiter, and fetal hypothyroidism documented by cord blood sampling, with intraamniotic thyroxine (250 μg weekly for 3 wk) resulting in resolution of the fetal hypothyroidism and the goiter (76). Other reports have suggested that simply stopping or reducing maternal antithyroid treatment, if the patient is euthyroid, may lead to resolution of fetal hypothyroidism (82, 102). Treatment of documented fetal thyrotoxicosis has in-

cluded beginning PTU in a euthyroid mother and modulating the dose by repeated cord blood sampling to determine fetal thyroid functions (84). In two other case reports, despite treatment of presumptive diagnoses of fetal thyrotoxicosis with maternal PTU treatment, both fetuses/neonates remained hyperthyroid after birth (85, 90). Finally, one case of fetal hyperthyroidism was treated successfully with maternal MMI (86). Of note, three of the four hyperthyroid fetuses in these case reports were from mothers with prepregnancy treatment of Graves' and/or a prior baby with neonatal Graves' disease. The fourth case was a woman who was poorly compliant with her antithyroid medication. In summary, the treatment for fetal hypothyroidism resulting from medical treatment of maternal Graves' includes decreasing or stopping maternal treatment and consideration of intraamniotic thyroxine. Treatment for fetal hyperthyroidism includes modulation of maternal antithyroid medication.

In both instances, and depending on the gestational age at diagnosis and the severity of fetal symptoms, delivery can be considered. In a recent prospective study of women with Graves' disease using ultrasound to assess for fetal goiter, fetal blood sampling was only done when noninvasive studies could not distinguish fetal hypothyroid from hyperthyroid disease in the presences of fetal goiter (102). Eleven fetal goiters were diagnosed and six fetuses received fetal blood sampling, which diagnosed fetal hypothyroidism in four and hyperthyroidism in two. Treatment of the seven fetuses with hypothyroidism (diagnosed presumptively or by fetal blood sampling) with reduction of the maternal ATD and in three fetuses intraamniotic injection of T_4 resulted in normalization of thyroid functions at birth in all but one neonate. In the four fetuses diagnosed with hyperthyroidism (two by clinical criteria and two by fetal blood sampling), increasing the maternal ATD resulted in a decrease in goiter size in all, but one fetus died *in utero*, and two neonates ultimately were diagnosed with neonatal Graves' disease.

2.4. RECOMMENDATIONS

2.4.a. Management of maternal hyperthyroidism: maternal aspects.

2.4.a.1. If a subnormal serum TSH concentration is detected during gestation, hyperthyroidism must be distinguished from both normal physiology of pregnancy and hyperemesis gravidarum because of the adverse effects of overt hyperthyroidism on the mother and fetus. Differentiation of Graves' disease from gestational thyrotoxicosis is supported by presence of clinical evidence of autoimmunity, a typical goiter, and presence of TRAb. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕) (62, 70, 71, 74, 75).

2.4.a.2. For overt hyperthyroidism due to Graves' disease or thyroid nodules, ATD therapy should be either initiated (for those with new diagnoses) or adjusted (for those with a prior history) to maintain the maternal thyroid hormone levels for free T_4 in the upper nonpregnant reference range. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕) (111, 142).

2.4.a.3. Because available evidence suggests that MMI may be associated with congenital anomalies, PTU should be used

as a first-line drug, if available, especially during first-trimester organogenesis. MMI may be prescribed if PTU is not available, or if a patient cannot tolerate or has an adverse response to PTU. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○) (105, 117–120, 143, 144).

2.4.a.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, or 3) a patient is nonadherent to ATD therapy and has uncontrolled hyperthyroidism. The optimal timing of surgery is in the second trimester. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (139, 140, 145).

2.4.a. 5. There is no evidence that treatment of subclinical hyperthyroidism improves pregnancy outcome, and treatment could potentially adversely affect fetal outcome. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (70, 71, 110, 111).

2.4.b. Management of maternal hyperthyroidism: fetal aspects.

2.4.b.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 the end of the second trimester in mothers with current Graves' disease or with a history of Graves' disease and treatment with 131-I or thyroidectomy before pregnancy, or with a previous neonate with Graves' disease. Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○) (82, 83, 99, 100, 102).

2.4.b.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. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕○○○). There are no data for or against recommending termination of pregnancy after 131-I exposure. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (133–137).

2.4.b.3. In women with elevated TRAb or in women treated with ATD, fetal ultrasound should be performed to look for evidence of fetal thyroid dysfunction, which could include growth restriction, hydrops, presence of goiter, advanced bone age, or cardiac failure. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○) (82, 99–102).

2.4.b.4. Umbilical blood sampling should be considered only if the diagnosis of fetal thyroid disease is not reasonably certain from the clinical data and the information gained would change the treatment. The USPSTF recommendation level is B; evidence is fair (GRADE 2|⊕○○○) (76, 82, 84, 85, 87–90, 102, 104, 146).

2.4.b.5. All newborns of mothers with Graves' disease should be evaluated by a medical care provider for thyroid dysfunction and treated if necessary. The USPSTF recom-mendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○) (99, 101, 102).

2.5. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

Berg GE, Nystrom EH, Jacobsson L, Lindberg S, Lindstedt RG, Mattsson S, Niklasson CA, Noren AH, Westphal OG 1998 Radioiodine treatment of hyperthyroidism in a pregnant women. J Nucl Med 39:2194–2195

A pregnant thyrotoxic woman received 500 MBq of 131-I in her 20th gestational week. The uptake at 24 h after administration was calculated to be 10 MBq (2%) in the fetal thyroid gland. The effective half-life was 2.5 d, giving a calculated absorbed dose to the fetal thyroid gland of 600 Gy (60,000 rads), which is considered to be an ablative dose. The calculated absorbed dose to the fetal body, including brain, was about 100 mGy (10 rads), and 40 mGy to the fetal gonads. Doses were estimated taking contributions from radioiodine in the mother, the fetal body and the fetal thyroid into consideration. At full term, an apparently healthy boy, having markedly raised cord blood serum TSH concentration and subnormal T_4 and low-normal T_3 concentrations, was born. Treatment with thyroxine was initiated from the age of 14 d. At 8 yr of age, the child attends regular school. A neuropsychological pediatric examination showed that the mental performance was within normal limits, but with an uneven profile. He has a low attention score and displays evidently subnormal capacity regarding figurative memory. Radioiodine treatment in pregnancy in the 20th gestational week does not give a total absorbed dose to the fetal body that justifies termination of pregnancy, but does give a high absorbed dose to the fetal thyroid.

Brodsky JB, Cohen EN, Brown BW, Wu ML, Whitcher C 1980 Surgery during pregnancy and fetal outcome. Am J Obstet Gynecol 138:1165–1167

The authors report 287 women who had surgery during pregnancy. Surgery during early pregnancy was associated with a significant increase in the rate of spontaneous abortion compared with the rate in a control group that did not have surgery. There were no differences in the incidence of congenital abnormalities in the offsprings of women who had surgery during early pregnancy. The data suggest that elective surgery be deferred during early pregnancy to minimize potential fetal loss.

Burrow GN 1985 The management of thyrotoxicosis in pregnancy. N Engl J Med 313:562–565

This is a review and includes recommendations for management of thyrotoxicosis in pregnancy and discusses indications for thyroid surgery in pregnancy.

Bydder SA, Clarke J, Semmens J, Joseph DJ 2005 Genetic counseling following paternal therapeutic irradiation. Australas Radiol 49:119–121

For the population, a doubling dose for hereditary effects of 1 Gy has recently been reaffirmed (United Nations Scientific Committee on the Effects of Atomic Radiation 2001).

However, a range of animal studies suggest conception with postmeiotic sperm carries a greater risk of genetic damage than conception with sperm derived from irradiated stem cells. The risks in this particular case were quantified. In male patients who are potentially fertile, the best advice remains to delay conception after radiotherapy for as long as 6 months.

Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG 2006 Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 107(2 Pt 1):337–341

All women who presented to Parkland Hospital for prenatal care between November 1, 2000, and April 14, 2003, underwent thyroid screening. Women with TSH values at or below the 2.5th percentile for gestational age and whose serum free T_4 levels were 1.75 ng/dl or less were identified to have subclinical hyperthyroidism. Those women screened and delivered of a singleton infant weighing 500 g or more were analyzed. Pregnancy outcomes in women identified with subclinical hyperthyroidism were compared with those in women whose TSH values were between the 5th and 95th percentiles. A total of 25,765 women underwent thyroid screening and were delivered of singleton infants. Of these, 433 (1.7%) were considered to have subclinical hyperthyroidism. Pregnancy complications and perinatal morbidity or mortality were not increased in women with subclinical hyperthyroidism. Results indicate that identification of subclinical hyperthyroidism and treatment during pregnancy is unwarranted.

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

This is a case report and summary of five other cases of choanal and esophageal atresia, scalp defects, and facial anomalies associated with first-trimester MMI exposure.

Cohen O, Pinhas-Hamiel O, Sivan E, Dolitski M, Lipitz S, Achiron R 2003 Serial *in utero* ultrasonographic measurements of the fetal thyroid: a new complementary tool in the management of maternal hyperthyroidism in pregnancy. Prenat Diagn 23:740–742

Fetal thyroid size was measured serially by transvaginal ultrasonography between 14 and 17 wk gestation and by abdominal ultrasonography between 18 and 37 wk gestation in 20 women with Graves' disease. Serial *in utero* ultrasonography measuring fetal thyroid size in mothers with Graves' disease can serve as an effective noninvasive tool for the early detection of enlarged fetal thyroid. When a dosage reduction does not cause a decrease in fetal thyroid size, transplacental passage of thyroid-stimulating antibodies causing fetal thyrotoxicosis should be suspected. (Clinical evaluation of 20 cases.)

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

Case report of a noncompliant woman with Graves' disease who presented thyrotoxic requiring a very high dose of PTU (900–1200 mg/d). She became pregnant on 800 mg/d

and presented for prenatal care at 17 wk. Fetal goiter was diagnosed at 28 wk. PTU dose was decreased and 250 μg thyroxine was given weekly intraaminiotically for 3 wk. The goiter resolved.

Davis LE, Lucas MJ, Hankins GDV, Roark ML, Cunningham FG 1989 Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol 160:63–70

The incidence of preterm labor increases as the degree of disease control worsens. Rates of congestive heart failure, fetal demise, small for gestational age infants and thyroid storm are increased in uncontrolled hyperthyroid women.

Di Gianantonio E, Schaefer C, Mastroiacovo P, Cournot M, Benedicenti F, Reuvers M, Occupati B, Robert E, Bellemin B, Addis A, Arnon J, Clementi M 2001 Adverse effects of prenatal methimazole exposure. Teratology 64:262–266

Outcome of 241 MMI first-trimester exposed pregnancies compared with 1089 non-MMI-exposed pregnancies prospectively studied. No increase in major anomalies or spontaneous abortion in MMI exposed group. Two neonates in MMI exposed group had choanal atresia or esophageal atresia and none in the control group did. Authors concluded based on this that choanal atresia and esophageal atresia may have higher incidence in MMI exposed neonates.

Fisher DA 1997 Fetal thyroid function: diagnosis and management of fetal thyroid disorders. Clin Obstet Gynecol 40: 16–31

This is a review paper on fetal thyroid function. Pertinent to its reference here, the paper reviews case series of treatment of fetuses with intraamniotic thyroxine for presumed hypothyroidism in cases of inadvertent maternal radioiodine treatment of Graves' disease between 10 and 20 wk gestation, or with fetal goiter. In several of these cases the intraamniotic thyroxine was associated with a reduction in goiter size. (Review and expert opinion.)

Goodwin TM, Montoro M, Mestman JH 1992 Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol 167:648–652

Sixty-six percent of 67 women admitted with hyperemesis gravidarum had biochemical hyperthyroidism [increased free thyroxine index (n = 39) or suppressed TSH (n = 40)] that was self-limited, resolving by 18 wk gestation. The severity of hyperemesis was found to vary directly with the degree of hyperthyroidism.

Greenberg F 1987 Brief clinical report: choanal atresia and athelia: methimazole teratogenicity or a new syndrome? Am J Med Genet 28:931–934

The author reports an infant girl with choanal atresia, athelia, minor anomalies, and mild to moderate mental retardation was born to a woman treated for hyperthyroidism throughout pregnancy with MMI and propranolol.

Johnsson E, Larsson G, Ljunggren M 1997 Severe malformations in infant born to hyperthyroid mother on methimazole. Lancet 350:1520

This is a case report of one woman treated with methimazol and other thyroid medications who delivered a baby at 27 wk with choanal atresia, esophageal atresia, and VSDs. The authors discuss the association of methimazol and fetal anomalies.

Laurberg P, Nygaard B, Glinoer D, Grussendorf M, Orgiazzi J 1998 Guidelines for TSH-receptor antibody measurements in pregnancy: results of an evidenced based symposium organized by the European Thyroid Association. Eur J Endocrinol 139:584–586

Expert panel of European endocrinologists reviewed 29 papers evaluating women with Graves' disease and neonatal risk for Graves'. Only nine papers fulfilled the following criteria: systematic investigation of more than 12 women with evaluation of neonatal thyroid function and contained new patient data. A total of 454 women and 462 pregnancies were included. The authors stated that 2–10% of newborns of mothers with Graves' disease will have neonatal Graves'. Authors present their recommendations based on these papers. However, no summary of the original data was presented.

Levinson G 2002 Anesthesia for surgery during pregnancy. In: Hughes SC, Levinson G, Rosen MA, eds. Anesthesia for obstetrics. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 249–265

This chapter in a major text on anesthesia for obstetric patients reviews the pertinent physiology of pregnancy relative to major surgery in pregnancy and reviews the risks of anesthetic medications in pregnancy.

Lowe SA 2004 Diagnostic radiography in pregnancy: risks and reality. Aust N Z J Obstet Gynaecol 44:191–196

Most diagnostic radiation procedures will lead to a fetal absorbed dose of less than 1 mGy for imaging beyond the abdomen/pelvis and less than 10 mGy for direct or nuclear medicine imaging. Potential adverse outcomes related to radiation exposure during pregnancy include teratogenicity, genetic damage, intrauterine death and increased risk of malignancy. The only adverse effect statistically proven at the dose levels associated with diagnostic radiation procedures is a very small increase in childhood malignancy, with an estimated increase of one additional cancer death per 1700 10 mGy exposures. The important exception was the risk to the fetal thyroid from radioiodine exposure after 12 wk gestation. In practice, diagnostic radiography during pregnancy not involving direct abdominal/pelvic high dosage is not associated with any significant adverse events. Counseling of pregnant women who require diagnostic radiographic procedures as well as those inadvertently exposed should be based on the available human data with an emphasis on the minimal impact of such procedures.

Martinez-Frias ML, Cereijo A, Rodriguez-Pinilla E, Urioste M 1992 Methimizole in animal feed and congenital aplasia cutis. Lancet 339:742–743

This is a letter to the editor of *Lancet* reporting that the Spanish Collaborative Study of Congenital Malformations reported a significant increase in children with aplasia cutis

that was not related to maternal MMI treatment. This trend occurred during the same time that in Spain there was increased use of illicit MMI in animal feed.

McKenzie JM. Zakarija M 1992 Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. Thyroid 2:155–163

Three different TRAb may occur in Graves' disease and Hashimoto's thyroiditis. TSAb can induce hyperthyroidism. The pathogenesis of Hashimoto's thyroiditis is largely cell-mediated immune destruction of the thyroid. However, in some patients the lack of goiter is associated with the presence in the blood of an antibody that inhibits the binding of TSH to its receptor (TSH-binding inhibiting antibody). This antibody prevents TSH from stimulating the thyroid and constitutes an explanation for hypothyroidism.

Mestman JH 2004 Hyperthyroidism in pregnancy. Best Pract Res Clin Endocrinol Metab 18:267–288

Graves' disease may complicate the course of pregnancy and pregnancy may alter the natural course of the thyroid disease. Women affected by the disease should be informed about the potential maternal and fetal problems if the condition is not properly managed. Preconception control of thyroid disease should be encouraged. Women suffering from hyperthyroidism or any other thyroid disease should be metabolically compensated at time of conception, and the need for contraception until the disease is controlled should be openly discussed. A multidisciplinary approach by a health care team is of paramount importance during pregnancy, with the involvement of the obstetrician, perinatologist, endocrinologist, neonatologist, pediatrician and anesthesiologist. In many situations the assistance of social workers, nutritionists, and other health care professionals may be needed. The future mother and her family should be aware of the potential complications for both mother and her offspring if proper management guidelines are not carefully followed.

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

Preeclampsia is twice as frequent in uncontrolled hyperthyroid women. Rates of congestive heart failure, fetal demise, small for gestational age infants and thyroid storm are increased in uncontrolled hyperthyroid women, and remain higher than control even in those women in whom control is achieved by delivery.

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

Two hundred thirty pregnancies in gravidas with Graves' disease were evaluated to try to identify risk factors for disorders of fetal growth and thyroid function. Neonatal thyroid function was assessed at birth and on d 5 of life. Fifteen neonates (6.5%) were small for gestational age at birth which was significantly associated with maternal thyrotox-

icosis lasting for at least 30 wk, TRAb levels of 30% or more at delivery, history of Graves' disease for at least 10 yr, and onset of Graves' disease before 20 yr of age. Thyroid dysfunction (overt thyrotoxicosis, chemical thyrotoxicosis, transient hypothyroidism, transient hyperthyroidism, central hypothyroidism) developed in 38 infants (16.5%) which was significantly associated with mothers total dose of antithyroid medication, duration of thyrotoxicosis in pregnancy, and TRAb level at delivery. With multivariate regression only TRAbs remained significantly associated with neonatal thyroid dysfunction. However, two of the six neonates with overt thyrotoxicosis had mothers with TRAbs in the negative range (<15%).

Momotani N, Noh J, Oyanagi H, Ishikawa N, Ito K 1986 Antithyroid drug therapy for Graves' disease during pregnancy. N Engl J Med 315:24–28

In 43 women with Graves' disease receiving ATD therapy until delivery, maternal free T_4 levels were closely correlated with cord levels. Some women with free T_4 levels in the laboratory normal reference range had babies with decreased free T_4 and elevated serum TSH levels.

Mortimer R, Cannell GR, Addison RS, Johnson LP, Roberts MS, Bernus I 1997 Methimazole and propylthiouracil equally cross the perfused human term placental lobule. J Clin Endocrinol Metab 82:3099–3102

Evaluated placenta passage in a isolated perfused term placenta of MMI and PTU. Both crossed the placenta easily with equilibrium reached at 2 h for both low and high doses of drug.

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

The authors report cord and neonatal thyroid function in infants born to women with active or remitted Graves' disease. Neonatal thyroid function and TSH-binding inhibitory immunoglobulin (TBII) levels are correlated with maternal TBII levels.

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

Of 40,000 deliveries, 24 pregnancies (26 fetuses) occurred in 18 women with Graves' disease. All pregnant women with Graves' disease underwent follow-up evaluations that included serial thyroid-stimulating antibody level, thyroid function, and ultrasound examinations. Umbilical blood sampling was recommended if the thyroid-stimulating antibody level was abnormally high or if fetal tachycardia, goiter, intrauterine growth retardation, or hydrops were present. Nine of 14 mothers with positive findings elected umbilical blood sampling. No complications were recorded in any of the 20 umbilical blood sampling. In women with Graves' disease, umbilical blood sampling in selected cases may improve the control of fetal thyroid function.

Peleg D, Cada S, Peleg A, Ben-Ami M 2002 The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. Obstet Gynecol 99:1040–1043

To determine whether risk of neonatal thyrotoxicosis was related to level of maternal thyroid-stimulating immunoglobulins (TSI) in women with Graves' disease the authors did a retrospective review of maternal TSI and risk of neonatal thyrotoxicosis over 10 yr. They found 29 women with 35 live births with Graves' disease and positive TSI. There were six cases of neonatal thyrotoxicosis (17%). A TSI of 5 index units or greater had a sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 76%, 40% and 100% for neonatal thyrotoxicosis.

Polak M, Le Gac I, Vuillard E, Guibourdenche J, Leger J, Toubert ME, Madec AM, Oury JF, Czernichow P, Luton D 2004 Fetal and neonatal thyroid function in relation to maternal Graves' disease. Best Pract Res Clin Endocrinol Metab 18:289–302

Authors describe an unpublished prospective study of 72 pregnant women with a history of Graves' disease. Fetal goiter was found at 32 wk in 11 of the fetuses of the 41 mothers with positive TSH-R antibodies and/or antithyroid treatment and in none of the fetuses of the 31 other mothers. Thyroid Doppler, bone maturation, fetal heart rate, and maternal antibody and ATD status effectively discriminated between hypothyroidism and hyperthyroidism. One fetus with hyperthyroidism died *in utero* at 35 wk from heart failure. Treatment was successful in the ten other fetuses.

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 offspring of a euthyroid mother, producing thyroid stimulating immunoglobulins. Ann Endocrinol (Paris) 58:338–342

Case report of three individual pregnancies in a euthyroid mother with a past history of Graves' disease and high levels of TSH-R stimulating antibodies. Fetal hyperthyroidism was suspected on the basis of fetal tachycardia, growth retardation, fetal goiter and fetal cord blood sampling confirmed high levels of free T_3, free T_4, suppressed fetal TSH levels, and high levels of fetal TRAb. Fetal cord blood sampling proved to be useful during these two pregnancies to ascertain the diagnosis of fetal hyperthyroidism and to monitor the dose of PTU administered to this euthyroid mother.

Porreco RP, Bloch CA 1990 Fetal blood sampling in the management of intrauterine thyrotoxicosis. Obstet Gynecol 76:509–512

A case report of a euthyroid patient with prior ablation for Graves' and a prior baby with Graves' disease in which repeated cord blood sampling was done to direct maternal treatment with PTU.

Stice RC, Grant CS, Gharib H, van Heerden JA 1984 The management of Graves' disease during pregnancy. Surg Gynecol Obstet 158:157–160

A retrospective review of records from 1960 through 1979 involving 25 pregnant women with thyrotoxicosis was per-

formed. Twenty-five patients were divided into three management groups, six managed medically, 10 surgically, and nine with a combination of medical and surgical therapy. Of the six patients managed medically, four were delivered of term infants and two had premature deliveries. Agranulocytosis developed in one of these women and one infant had a fetal goiter. Of the 10 patients surgically managed, three underwent spontaneous abortions, four were delivered of term infants and two had premature deliveries. Of the nine patients who failed to respond to medical treatment and subsequently underwent operation, eight were delivered of term infants. Of the 19 surgically treated patients, one patient had permanent injury to the recurrent laryngeal nerve and one had temporary hypoparathyroidism. The authors concluded that either medical or surgical treatment was is safe and effective.

Tan JY, Loh KC, Yeo GS, Chee YC 2002 Transient hyperthyroidism of hyperemesis gravidarum. BJOG 109:683–688

The authors monitored thyroid function in 39 women with hyperemesis gravidarum and thyrotoxicosis. Free T$_4$ levels normalized by 15 wk gestation in the 39 women with transient hyperthyroidism, whereas TSH remained suppressed until 19 wk gestation. None of these women were clinically hyperthyroid. In transient hyperthyroidism of hyperemesis gravidarum, thyroid function normalizes by the middle of the second trimester without antithyroid treatment.

Van Dijke CP, Heydendael RJ, De Kleine MJ 1987 Methimazole, carbimazole and congenital skin defects. Ann Intern Med 106:60–61

This is a case report and review of the literature discussing a total of 11 cases of an association between maternal use of methimazol and congenital scalp defects. The authors also analyzed data from all infants with congenital scalp defects born in one hospital from 1959 to 1986. There were 13 cases of scalp defects for a rate of 0.03%. None of these mothers were on methimazol. During this same time period they had 24 mothers with first-trimester exposure to methimazol or carbimazol and they had no infants with scalp defects.

Van Kamp IL, Klumper FJ, Oepkes D, Meerman RH, Scherjon SA, Vandenbussche FP, Kanhai HH 2005 Complications of intrauterine intravascular transfusion for fetal anemia due to maternal red-cell alloimmunization. Am J Obstet Gynecol 192:171–177

Cohort study of 254 fetuses treated with 740 intrauterine transfusions. Procedure related complications were delineated. The total procedure related complication rate was 3.1% and the procedure related fetal loss rate was 1.6%.

Wallace C, Couch R, Ginsberg J 1995 Fetal thyrotoxicosis: a case report and recommendations for prediction, diagnosis, and treatment. Thyroid 5:125–128

This is a report of one case of fetal hyperthyroidism diagnosed in a woman who had been previously treated with RAI to ablate her thyroid and was euthyroid on thyroxine. A presumptive diagnosis of fetal thyrotoxicosis was made based on fetal tachycardia and high level of maternal TSI. Maternal PTU was started but the patient delivered spon-

taneously and the neonate was hyperthyroid. The authors proposed a guideline.

Wenstrom KD, Weiner CP, Williamson RA, Grant SS 1990 Prenatal diagnosis of fetal hyperthyroidism using funipuncture. Obstet Gynecol 76:513–517

A case report of two cases of fetal hyperthyroidism in one woman with a previously affected baby and another poorly compliant woman with Graves' disease. Cord blood analysis was used to document abnormal fetal thyroid function and both women were treated with antithyroid medication. The euthyroid patient also received thyroxine. One case resulted in successful treatment.

Wilson LC, Kerr BA, Wilkinson R, Fossard C, Donnai D 1998 Choanal atresia and hypothelia following methimazole exposure *in utero*: a second report. Am J Med Gen 75:220–222

The authors describe a 3-yr-old boy with bilateral choanal atresia, hypoplastic nipples, and developmental delay who had been exposed to carbimazole *in utero* because of maternal Graves' disease.

Zanzonico PB 1997 Radiation dose to patients and relatives incident to 131I therapy. Thyroid 7:199–204

This is a review of the 131-I dosing and effects on relatives. The key information in this paper is that the fetal thyroid gland begins to be able to concentrate iodine at 10–12 wk gestation and therefore maternal exposure to 131-I after 10 wk is associated with fetal hypothyroidism including cretinism. Exposure before 10 wk did not affect fetal outcome.

Zimmerman D 1999 Fetal and neonatal hyperthyroidism. Thyroid 9:727–733

Fetal hyperthyroidism may be associated with intrauterine growth retardation, nonimmune fetal hydrops, craniosynostosis, and intrauterine death. Features of this condition in the neonate include hyperkinesis, diarrhea, poor weight gain, vomiting, ophthalmopathy, cardiac failure and arrhythmias, systemic and pulmonary hypertension, hepatosplenomegaly, jaundice, hyperviscosity syndrome, thrombocytopenia, and craniosynostosis. The time course of thyrotoxicosis depends on etiology. Treatment of fetal hyperthyroidism comprises administration of ATDs to the mother. Fetal heart rate and fetal growth should be monitored. Hyperthyroid neonates may be treated with ATDs, β-adrenergic receptor blocking agents, iodine, or iodinated contrast agents, and at times, with glucocorticoids and digoxin. (Clinical review.)

SECTION 3. GESTATIONAL HYPEREMESIS AND HYPERTHYROIDISM

3.2. BACKGROUND

Thyroid hormone economy, secretion, and measurements are affected by normal pregnancy. Vomiting occurs in normal pregnancy during the first trimester and usually ceases by the 15th wk. Severe vomiting in early pregnancy that causes more than 5% weight loss, dehydration, and ketonu-

ria is defined as hyperemesis gravidarum and occurs in 0.5–10 cases per 1000 pregnancies (147). Hyperemesis is associated with high hCG levels occurring at this time, but the exact cause remains uncertain. The condition can cause severe morbidity, and require treatment with fluids, electrolytes, vitamins, and other medications. By definition, these women do not have molar pregnancy or choriocarcinoma. It is common and normal for TSH to be suppressed below the nonpregnant lower limit at this time, because of the thyroid stimulating activity of hCG. However, 30–60% of patients with hyperemesis gravidarum have elevations of free thyroid hormone concentrations along with suppressed TSH (70, 148, 149). Women with hyperemesis and elevated thyroid hormone levels most commonly do not have other clinical evidence of Graves' disease and lack the antibodies to the thyroid typically present in Graves' disease (70, 71, 148, 150, 151). A small portion of these patients have clinical hyperthyroidism, termed gestational hyperthyroidism (70, 71). Of course Graves' disease can also occur coincident with hyperemesis (71). As well, many common signs and symptoms of hyperthyroidism may be mimicked by normal pregnancy. The clinical challenge is to differentiate these disorders.

In normal pregnancy, when hCG levels are highest at 10–12 wk gestation, there is suppression of serum TSH levels, presumably due to slight increases in free thyroxine concentration driven by high hCG values (152). In twin pregnancies, hCG levels tend to be higher and suppressed TSH levels are more frequent (153). These abnormalities are exaggerated in hyperemesis gravidarum and more so in gestational hyperthyroidism, especially if peak hCG values exceed 75–100,000 IU/ml with a duration of the peak that exceeds the normal situation (which is less than 1 wk). The etiology of thyroid stimulation is thought to be hCG itself, or molecular variant proteins related to hCG (79, 152, 154, 155). Human chorionic gonadotropin (hCG) is a weak TSH agonist (154). In FRTL-5 rat thyroid cells, hCG increases cAMP, iodide transport, and cell growth (154). Human CG has thyroid-stimulating activity in bioassays in mice and in clinical studies in man (154). In cultured cells transfected with the human TSH-R, hCG increases generation of cAMP (155). Great elevations of hCG occurring in patients with hydatiform mole or choriocarcinoma are often associated with clinical hyperthyroidism (154). Molecular variants of hCG with increased thyrotropic potency have been detected (79, 154). Because the elevations of thyroid hormone and suppression of TSH are not entirely correlated with hCG levels, other factors must also help determine the response to hCG.

Inherited or *de novo* TSH-R mutations with functional hypersensitivity to hCG have also been recognized as a rare cause of gestational hyperthyroidism (156).

3.3. EVIDENCE

3.3.1. Diagnosis.
Gestational hyperthyroidism is characterized by elevated free T_4 and T_3 levels, suppressed TSH, variable evidence of clinical hyperthyroidism, usually minimal thyroid enlargement, and absence of antithyroid antibodies (70, 71, 151). Graves' disease is suggested by prior personal history of hyperthyroidism, goiter, more obvious clinical hyperthyroidism, and is strongly supported by dem-

onstration of antibodies to TSH-R (receptor). Although TSH-R stimulating antibodies are specific for Graves' hyperthyroidism, antibodies binding to TSH-R (binding antibodies) are more commonly measured and are highly suggestive of Graves' disease, if positive. TG-Ab and TPO-Ab indicate the presence of autoimmune thyroid disease, but are not diagnostic of Graves' disease. A family history of Graves' disease is also suggestive evidence.

There is disagreement as to whether thyroid hormone should be measured 1) in all pregnancies with hyperemesis, or 2) only when clinical features of hyperthyroidism are present. Because most women with hyperemesis gravidarum will have chemical evidence of hyperthyroidism but do not have clinical hyperthyroidism that requires treatment, and they recover spontaneously (70, 71, 151, 152), it may be argued that measurement of thyroid function is unnecessary. However, some patients appear to clearly benefit from antithyroid therapy, and some patients have coincident Graves' disease that can cause both maternal and fetal complications unless appropriately treated (see *Section 2*). Although no perfect evidence proving this point is available, it is generally suggested to measure thyroid hormone levels and TSH in patients with gestational hyperemesis, and certainly in any patient suspected of having clinical hyperthyroidism (70, 149, 157, 158). A prospective study was conducted on Saudi healthy pregnant women (n = 406) at 12–15 wk of gestation, who were compared with healthy nonpregnant controls. Suppressed levels of serum TSH (<0.30 μU/ml) were found in 11.1% of pregnant women. This was accompanied by significant increases in free thyroxine ($P < 0.001$), free triiodothyronine ($P < 0.05$), hCG ($P < 0.001$), and β-subunit of hCG ($P < 0.001$). A significant negative correlation was found between serum levels of TSH and hCG (r = -0.381) (159).

In general practice measurement of free T_4 or free T_3 is more useful than total T_4 or total T_3. However, the TBG changes in pregnancy may make the free hormone tests less reliable or more difficult to interpret. Because pregnancy with elevated TBG has known and predictable effects on T_4 and T_3 assays, it may be preferable to measure total T_4 with interpretation of the results adjusted for the range found in normal pregnancy (1.5 times the nonpregnant range). (See also discussion in *Sections 1.2.2 and 2.3.1*.)

3.3.2. Treatment.
No data are available to designate exactly which patients should be treated with antithyroid medication. Most patients with gestational hyperthyroidism do not have obvious clinical symptoms of hyperthyroidism, and spontaneous recovery of thyroid hormone levels to normal usually occurs. Close observation of the course of the clinical presentation and thyroid hormone abnormalities is indicated. Some authors suggest giving antithyroid therapy to patients with symptomatic hyperthyroidism and severely elevated T_4 and/or T_3 ($T_4 > 50\%$ over pregnancy-adjusted "normal" values). Therapy may often be discontinued, if the hyperemesis subsides, by mid-gestation. If Graves' disease is considered to be the cause, antithyroid treatment may be needed for the duration of pregnancy, with awareness that there is often spontaneous improvement in Graves' disease

during the second and early third trimester as a result of reduced immunological stimulation.

In a study of 44 women with hyperemesis and elevated free thyroid hormone levels, five women were diagnosed with Graves' disease based on clinical features and positive thyroid stimulating antibody. The remainder were thought to have gestational thyrotoxicosis, and in these patients free T_4 levels normalized by 15 wk, whereas TSH remained suppressed until 19 wk gestation. None of these women was clinically hyperthyroid. Thyroid antibodies were not found in most instances. The median birth weight of the infants of mothers who experienced a weight loss of more than 5% of their prepregnancy weight was lower than that of infants of women who did not (71).

In another study 22 of 33 patients admitted with hyperemesis (66.7%) had biochemical hyperthyroidism (suppressed TSH or increased T_3 index or T_4 index). Hyperthyroid patients were more likely than euthyroid patients to have abnormal electrolyte levels [16/22 (72.7%) *vs.* 3/1 (27.3%), $P < 0.02$] or increased liver enzyme levels [8/22 (36.4%) *vs.* 3/11 (27.3%)]. The severity of hyperemesis was found to vary directly with the degree of hyperthyroidism. A predominance of females was found among the offspring of mothers with hyperemesis gravidarum (149).

Treatment of subclinical hyperthyroidism (TSH below normal limits with free T_4 and total T_4 in the normal pregnancy range) has not been found to improve pregnancy outcome and may risk unnecessary exposure of the fetus to ATDs (70, 71, 110, 111).

3.4. RECOMMENDATIONS

3.4.1. Thyroid function tests should be measured in all patients with hyperemesis gravidarum (5% weight loss, dehydration, and ketonuria). The USPSTF recommendation level is B; evidence is poor (GRADE 2|⊕○○○) (70, 71, 152, 158).

3.4.2. Few women with hyperemesis gravidarum will require ATD treatment. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕). Overt hyperthyroidism believed due to coincident Graves' disease should be treated with ATDs. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○). Gestational hyperthyroidism with clearly elevated thyroid hormone levels (free T_4 above the reference range or total $T_4 > 150\%$ of top normal pregnancy value and TSH < 0.1 μU/ml) and evidence of hyperthyroidism may require treatment as long as clinically necessary. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (70, 71, 152, 158).

3.5. REMARKS

Although the data available do not prove the benefit, many members of this committee believe that there is significant potential benefit in performing thyroid function testing on all pregnant women with hyperemesis and possible hyperthyroid signs and symptoms, and that there is likely benefit from screening all women with gestational hyperemesis.

3.6. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

Al-Yatama M, Diejomaoh M, Nandakumaran M, Monem RA, Omu AE, Al Kandari F 2002 Hormone profile of Kuwaiti women with hyperemesis gravidarum. Arch Gynecol Obstet 266:218–222

Human CG, TSH, total T_4, and free T_4 were measured in the serum of 55 patients with hyperemesis gravidarum compared with a control group of 55 women. The incidence of hyperemesis in the maternity population was 45 per 1000 deliveries. Total (β)hCG and total T_4 and free T_4 were significantly higher in the hyperemesis patients than in the normal controls ($P < 0.0001$, $P = 0.004$, and $P = 0.01$, respectively). TSH levels were significantly lower in hyperemesis patients than in their normal controls ($P < 0.0001$). None of the patients showed signs of hyperthyroidism.

Goodwin TM, Montoro M, Mestman JH 1992 Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol 167:648–652

Sixty-seven patients seen at Los Angeles County Women's Hospital over a 10-month period with hyperemesis gravidarum were studied prospectively with respect to thyroid function. Forty-four patients (66%) had biochemical hyperthyroidism [increased free thyroxine index (n = 39) or suppressed TSH (n = 40)] that was self-limited, resolving by 18 wk gestation. Hyperthyroid patients were more likely than euthyroid patients to have abnormal electrolyte levels [23/39 (59%) *vs.* 6/28 (21%)] and increased liver enzyme levels [23/59 (59%) *vs.* 5/28 (18%), $P < 0.01$]. The severity of hyperemesis was found to vary directly with the degree of hyperthyroidism. Hyperthyroidism is a common, self-limited finding in hyperemesis. The cause of the hyperthyroidism may be linked to the cause of hyperemesis itself.

Goodwin TM, Montoro M, Mestman JH, Pekary AE, Hershman JM 1992 The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 75:1333–1337

The relationship of serum hCG, thyroid function, and severity of vomiting among 57 hyperemesis patients and 57 pregnant controls matched for gestational age was studied. TSH was suppressed in 60% of hyperemesis patients and 9% of controls. HCG correlated directly with free T_4 (r = 0.45, $P < 0.001$) and inversely with TSH (r = −0.48, $P < 0.001$). Hyperemesis patients had significantly greater mean serum hCG, free T_4, total T_3, and estradiol, and lesser serum TSH compared with controls. The degree of biochemical hyperthyroidism and hCG concentration varied directly with the severity of vomiting. Unextracted serum was tested for thyrotropic activity by measuring its effect on iodide uptake in cultured FRTL-5 rat thyroid cells. Thyrotropic activity correlated with serum hCG (r = 0.50, $P < 0.001$). These data show that biochemical hyperthyroidism is a common finding in patients with hyperemesis gravidarum and suggest that hCG is the thyroid stimulator in this state. The increased estradiol concentration in patients with hyperemesis gravi-

darum may be attributed to the effects of hCG on steroidogenesis.

Lazarus JH 2005 Thyroid disorders associated with pregnancy: etiology, diagnosis, and management. Treat Endocrinol 4:31–41

Clinical review.

Tan JY, Loh KC, Yeo GS, Chee YC 2002 Transient hyperthyroidism of hyperemesis gravidarum. BJOG 109:683–688

Data are summarized in *Section 3.3.2.*

SECTION 4. AUTOIMMUNE THYROID DISEASE AND MISCARRIAGE

4.2. BACKGROUND

4.2.1. Miscarriage and pregnancy. Thirty-one percent of all pregnancies end in miscarriage (160). In general, women who have a single pregnancy loss do not undergo an evaluation for the cause of the miscarriage. On the other hand, women who experience recurrent abortion (0.3–5% of women), defined as three or more spontaneous miscarriages without an intervening live birth, are thoroughly evaluated for an underlying etiology (161, 162). The cause of pregnancy loss is apparent in approximately 50% of recurrent aborters and includes, but is not limited to, infection, autoimmune disease, exposure to drugs, alcohol and tobacco, obesity, aneuploidy, thrombophilias, medical diagnoses such as endocrine disease and inflammatory bowel disease, endometrial defects, and pelvic anatomic abnormalities.

4.2.2. Association of miscarriage and autoimmune thyroid disease. Since an association between TAI and miscarriage was first reported in 1990 (163, 164), a body of literature has evaluated the relationship between thyroid antibodies and miscarriage in various populations of pregnant women.

4.3. EVIDENCE

4.3.1. Increased risk of miscarriage in euthyroid women in unselected populations with autoimmune thyroid disease. A number of studies have examined the risk of miscarriage in patients with autoimmune thyroid disease. Stagnaro-Green *et al.* (164) screened 552 women in the first trimester of pregnancy for thyroid antibodies. Women who were thyroid antibody positive miscarried at a rate of 17% compared with 8.4% for the autoantibody-negative women. The increase in miscarriage was unrelated to the presence of cardiolipin antibodies. Glinoer *et al.* (163) examined 120 euthyroid pregnant women with a history of thyroid disease or with some form of thyroid abnormality; one group (n = 45) was positive for thyroid autoantibodies. This group had an increased risk of spontaneous abortion (13% *vs.* 3%). IIjima *et al.* (165) similarly examined almost 1200 pregnant women for the presence of antithyroid antibodies, ANA, anti-double-stranded DNA and rheumatoid factor. They found that patients positive for antithyroid microsomal antibody had a 2-fold increased incidence of spontaneous loss and those positive for ANA had a 3-fold increased loss rate. The study of Bagis *et*

al. (166) reported on the risk of miscarriage and the prevalence of autoimmune thyroid antibody-positive women. Of almost 900 women completing the study, 12.3% were thyroid antibody (TPO, TG autoantibody) positive; this group was 3.5 times more likely to report a history of miscarriage than was the thyroid antibody-negative group.

In conclusion, an association exists between thyroid antibodies and miscarriage in an unselected population. It should be noted that causality has not been established. Thyroid antibodies may simply serve as a marker for autoimmune disease. Furthermore, few studies examined the antiphospholipid antibody (APLA) status of women who miscarried, and none of the studies investigated for other known causes of miscarriage.

4.3.2. Autoimmune thyroid disease in euthyroid women with recurrent miscarriages. A number of studies have investigated the relationship between thyroid antibodies and recurrent miscarriage. Pratt *et al.* (167) examined 42 nonpregnant women with a history of recurrent miscarriage, and followed their outcome in the subsequent pregnancy. Of the 42 women, 31% (n = 13) were positive for antithyroid antibodies. Twelve of the 42 women experienced an abortion with the next pregnancy. Sixty-seven percent (8/12) of the women who aborted were thyroid antibody positive *vs.* an antibody positivity rate of only 17% (5/30) in the women who carried to term. The study is limited by lack of attention to other causes of recurrent miscarriage. Bussen and Steck (168) examined 22 nonpregnant patients with the diagnosis of recurrent abortion for the presence of antithyroid antibodies, comparing them with 22 multiparous patients and 22 nulliparous patients without known endocrine disorders. Thirty-six percent of those with a history of recurrent miscarriages were positive for antithyroid antibodies *vs.* 9% and 5% among the multiparous and nulliparous control groups. Markers for other immune disorders were not sought. The authors concluded that antithyroid antibodies may be a marker for autoimmune mediated recurrent miscarriage.

In contrast, Esplin *et al.* (169) tested for TG- and TPO-Ab in 74 nonpregnant patients historically remarkable for recurrent miscarriage; the controls were 75 healthy women of similar gravidity. Samples were obtained at least 6 months after a pregnancy. Twenty-nine percent of recurrent miscarriage patients and 37% of the control group were positive for one or both of the antibodies tested ($P > 0.05$). All were euthyroid. The authors concluded that those with a history of recurrent miscarriage were no more likely than the control population to test positive for antithyroid antibodies. Rushworth *et al.* (170) examined the prevalence of thyroid autoantibodies in 870 patients with the diagnosis of recurrent miscarriage in whom normal parental karyotypes were established. In the euthyroid, antibody-positive group, the subsequent pregnancy success rate was 58%, as it was for the antibody-negative group. The authors also concluded that the risk of subsequent pregnancy loss in women with recurrent miscarriage was unaffected by their thyroid antibody status.

De Carolis *et al.* (171) reported on 203 patients with APLAs and 162 with antithyroid antibodies, all of whom had a diagnosis of recurrent miscarriage. Upon further testing of

the patients with APLA, 54 were found to also have anti-thyroid antibodies. Forty-eight to 74% of these patients achieved pregnancy. Pregnancy outcome was available in 46% of the women who became pregnant. Of patients with outcomes available, it appears as if outcome with APLA alone (60/149 followed; 55/60 successful pregnancies) is better than that in patients with APLA and antithyroid antibodies (25/54 followed; 15/25 successful pregnancies), which in turn is similar to that with antithyroid antibodies alone (14/162 followed; 8/14 successful pregnancies). The authors concluded that their results support an investigation for antithyroid antibodies in APLA patients with recurrent miscarriages.

In conclusion, the majority of studies demonstrate an association between thyroid antibodies and miscarriage in euthyroid women with recurrent miscarriage. It should be noted, however, that the strength of the association is not as robust as is the relationship between thyroid antibodies and miscarriage in an unselected population.

4.3.3. Autoimmune thyroid disease in women undergoing assisted reproductive technology (ART). Six studies have examined whether the miscarriage rate is higher in infertility patients undergoing ART, according to the presence or absence of thyroid antibodies. Four studies (172–175), two of which were prospective and two retrospective, showed a 2- to 3-fold difference in miscarriage rates in thyroid antibody-positive *vs.* thyroid antibody-negative patients, but the other two (176, 177), one of which was prospective and one retrospective, did not. In a prospective series by Poppe *et al.* (174), nine of 17 women with TPO-Ab miscarried (53%) *vs.* 20 of 87 (23%) without antibodies ($P = 0.02$). In the prospective study by Negro *et al.* (173) in which 72 thyroid antibody-positive women *vs.* 412 thyroid antibody-negative women underwent ART, the miscarriage rate was higher in the antibody-positive group than in the negative group (42% *vs.* 26%, $P < 0.05$). Treatment with levothyroxine did not improve the miscarriage rate when half of the thyroid antibody-positive group was randomized to receive 1 μg/kg·d. In a retrospective cohort of 487 women who successfully conceived with ART (175), 32% of the 106 thyroid antibody-positive patients miscarried *vs.* 16% of the 381 antibody-negative patients, a difference that did reach statistical significance. A very small retrospective study by Kim *et al.* (172) detected a 40% miscarriage rate in the ten thyroid antibody-positive patients who became pregnant with *in vitro* fertilization (IVF) compared with an 11% miscarriage rate in the 35 antibody-negative patients who became pregnant.

In contrast to the above studies, a small prospective series by Muller *et al.* (177) failed to find a difference in the miscarriage rate between thyroid antibody-positive and antibody-negative women undergoing ART. There was no statistical difference between the miscarriage rate (33%) in the 12 antibody-positive women who became pregnant and that (19%) of the 42 antibody-negative women, although a trend toward a higher miscarriage rate was noted in the thyroid antibody-positive women. The largest series, although retrospective, failed to demonstrate an adverse effect on miscarriage rates in antibody-positive *vs.* -negative women undergoing ART (176). Of 143 thyroid antibody-positive

women, the miscarriage rate was precisely the same (46%) as that of the 730 antibody-negative women.

The prevalence of thyroid antibodies in women undergoing ART was examined in four studies (173–176) and found to range between 14% and 22%, which is not statistically different from the prevalence of antibodies in women not undergoing ART. Pregnancy rates have also been examined (172, 174, 177–179) in women undergoing ART with positive thyroid antibodies compared with women with negative thyroid antibodies. The results are conflicting. In the two largest studies, Poppe *et al.* (174) and Muller *et al.* (177) found no difference in pregnancy rates in thyroid antibody-positive *vs.* thyroid antibody-negative women undergoing ART and actually a trend toward higher pregnancy rates in the antibody-positive women. However, Kim *et al.* (172) and Geva *et al.* (179) found that pregnancy rates were lower by approximately 1.5- to 2-fold in the thyroid antibody-positive women than in those without antibodies. Bussen (178), in a small case control study, also found that women who failed to conceive after three cycles of IVF and embryo transfer were more likely to be thyroid antibody positive compared with a control group of women who had been enrolled for ART, but the authors did not report the pregnancy rates in their control group.

In conclusion, the literature on pregnancy loss in thyroid antibody-positive women who undergo ART is mixed. The methods of ART are not consistent between the series nor are the causes of infertility controlled for among studies. Given that four of the six studies did find a relationship, there is a suggestion in the literature that a relationship exists between TAI and pregnancy loss in this subgroup of women. However, it is too early to draw a definitive conclusion.

4.3.4. Medical intervention in thyroid antibody-positive women with recurrent abortion. Four studies have investigated whether intervention in thyroid antibody-positive women with recurrent abortion would decrease the miscarriage rate. Each of the four studies demonstrated a beneficial impact of intervention. The study design of each of the papers severely limits the ability to draw conclusions regarding the impact of intervention.

Kiprov *et al.* (180) studied 35 women with recurrent abortion who expressed autoimmune antibodies. All women had been screened for known causes of miscarriage and none had an alloimmune reaction to paternal lymphocytes. Twenty-four of the patients (69%) were thyroid antibody positive and six patients had anticardiolipin antibodies. Four women presented with both antithyroid and anticardiolipin antibodies. All women were administered intravenous immunoglobulin (IVIG) before conception and every 3 wk for the first 8 months of gestation. Eighty percent (28/35) of the women had a successful pregnancy. The study did not include a control group.

Sher *et al.* (181) evaluated the impact of IVIG therapy in women undergoing IVF who exhibited thyroid antibodies. Eighty-two APLA-negative women were divided into two groups. Thirty-seven women received heparin/aspirin, and 45 received heparin/aspirin and IVIG. The live birth rate in the IVIG group was 51% compared with 27% in the heparin/

aspirin control group ($P = 0.027$). The study was not double blinded.

In 2000, Stricker *et al.* (182) studied 47 women with recurrent abortion who were at least 28 yr old. Secondary causes of recurrent spontaneous abortion were excluded and all women had a panel of immunological tests performed. Fifty-three percent of the women were positive for antithyroid antibodies and 32% exhibited anticardiolipin antibodies. All patients were offered IVIG therapy, with 11 patients refusing therapy. Two thirds (24/36) of the women who received IVIG became pregnant, with 92% carrying to term (22/24). Seven of the 11 women who refused IVIG conceived; however, all experienced miscarriages in the first trimester. The study was not randomized and outcome for the women who were thyroid antibody-positive was not reported.

Vaquero *et al.* (183) investigated the impact of intervention on 42 women with thyroid abnormalities and a minimum of two first-trimester miscarriages. Eleven thyroid antibody-positive women were treated with IVIG, 16 thyroid antibody-positive women were given desiccated thyroid, and 15 women with abnormal TRH stimulation tests were given thyroid hormone. Full-term delivery rate was 93% in the abnormal TRH group, 81% in the antibody-positive group given desiccated thyroid, and 55% in the IVIG group. The study was not randomized, the sample size was limited, and there was no control group.

In conclusion, the studies reviewed demonstrate that intervention with either thyroxine or IVIG may decrease the miscarriage rate in women with recurrent abortion who are thyroid antibody-positive. 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 in recurrent aborters who exhibit TAI.

Finally, a single study has evaluated the impact of thyroxine therapy in euthyroid antibody-positive infertile women who underwent assisted reproduction techniques (173). Although the miscarriage rate was lower in women who received thyroxine (33%) than in those who did not (52%), this difference failed to reach statistical significance (which may have been secondary to the small sample size).

4.3.5. Medical intervention in thyroid antibody-positive women with no prior history of pregnancy loss. Negro *et al.* (21) performed a prospective, randomized trial of 984 unselected women who were screened for TPO-Ab positivity and thyroid function tests at the first obstetrical visit. The 115 women who were TPO-positive were divided into two groups: Group A (n = 57) included TPO+ women treated with levothyroxine; Group B (n = 58) included TPO+ women who received no levothyroxine intervention. Group C (n = 869) consisted of all TPO antibody-negative women, none of whom received levothyroxine. Outcome parameters of the study included spontaneous pregnancy loss and preterm delivery (delivery before 37 wk gestation). The miscarriage rate was significantly higher in Group B (13.8%) than in Group A (3.5%) or C (2.4%) ($P < 0.05$). Similarly, the preterm delivery rate was higher in Group B (22.4%) than in Group A (7%) or C (8.2%) ($P < 0.05$).

4.4. RECOMMENDATIONS

4.4.1. Although 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 this date, only one adequately designed intervention trial has demonstrated a decrease in the miscarriage rate in thyroid antibody-positive euthyroid women. The USPSTF recommendation level is C; evidence is fair (GRADE 2|⊕○○○) (164, 171, 181).

4.5. REMARKS

None.

4.6. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

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   Data are summarized in *Section 4.3.4.*

Stagnaro-Green A, Roman SH, Cobin RC, El-Harazy E, Alvarez-Marfany M, Davies TF 1990 Detection of at risk pregnancy using highly sensitive assays for thyroid autoantibodies. JAMA 264:1422–1425
   Stagnaro-Green *et al.* screened 552 women in the first trimester of pregnancy for thyroid antibodies. Women who were thyroid antibody positive miscarried at a rate of 17% compared with 8.4% for the autoantibody-negative women. The increase in miscarriage was unrelated to the presence of cardiolipin antibodies.

SECTION 5. THYROID NODULES AND CANCER
5.2. BACKGROUND

5.2.1. Incidence and growth of thyroid nodules. Three studies have evaluated the incidence of thyroid nodularity during pregnancy. Each study was performed in either an area of mild iodine insufficiency or borderline iodine sufficiency. Glinoer *et al.* (163) performed a prospective study in pregnant women with mild thyroid abnormalities from Brussels, an area of mild iodine insufficiency. Twenty thyroid antibody-negative women had thyroid nodules detected by sonography on initial presentation during pregnancy. Repeat ultra-

sound performed 3 d postpartum revealed a 60% increase in the size of the nodules and the detection of new nodules in 20% of the women (n = 4).

Struve *et al.* (184) performed thyroid ultrasounds in Northern Germany, an area of iodine insufficiency. The women, based on their obstetrical history, were divided into four groups of 53 women each (total n = 212). The groups consisted of women with no prior pregnancies, one pregnancy, two pregnancies, or three or more pregnancies. The prevalence of thyroid nodularity was significantly greater in women with a history of prior pregnancies than in women with no previous pregnancies (25.1% *vs.* 9.4%, $P < 0.05$). Furthermore, women with three or more pregnancies had a higher percentage of thyroid nodules than women who had one or two prior pregnancies (33.9% *vs.* 20.7%, $P < 0.05$).

Kung *et al.* (185) prospectively followed 212 women from Southern China, an area of borderline iodine sufficiency, throughout the three trimesters of pregnancy as well at and 1.5 and 3 months postpartum. Nodules were detected in 15.3% (n = 34) of women at 12–14 wk gestation. Although the diameter of the nodules remained constant throughout pregnancy, a significant increase in nodule volume was detected. New nodules were detected during pregnancy in 11.3% (n = 25) of the cohort.

In conclusion, in areas of mild iodine insufficiency or borderline iodine sufficiency, preexisting nodules are prone to increase in size during pregnancy. Furthermore, during the course of pregnancy, new nodules will be detected in approximately 15% of women. Data on nodule growth and formation in iodine replete areas are not available.

5.2.2. Diagnostic approach to thyroid nodules in pregnancy. The diagnostic evaluation of a thyroid nodule discovered during pregnancy should be similar to that of nonpregnant patients, but the ongoing pregnancy raises specific concerns regarding timing of surgical management (186–190). Thyroid function tests should be performed, searching for hypothyroidism or hyperthyroidism. In certain circumstances, evaluating for thyroid autoantibodies or checking a serum calcitonin level may be useful, the latter when there is any suspicion of medullary thyroid cancer. Radionuclide scanning of the thyroid is contraindicated during pregnancy.

Diagnosis and decision-making for treatment and overall management in the context of a nodule diagnosed in pregnancy relies primarily on the results of thyroid ultrasound and fine needle aspiration (FNA) biopsy (FNAB). Despite the fact that the minority (5–20%) of thyroid nodules are malignant, the fear of cancer may be accentuated in pregnant women. Therefore, in most pregnant women, diagnostic investigation using FNAB is recommended (186, 191). Although delay in the work-up of a nodule until after delivery causes no change in final prognosis as compared with surgical resection of a malignant lesion in the second trimester (188, 192), knowing the diagnosis via FNA cytology is often helpful to the mother in planning the postpartum course, including decisions regarding breast-feeding and the potential need for adjunctive therapy with radiodiode after surgical removal of a cancer.

As is the case outside of pregnancy, thyroid ultrasound is useful to characterize the dominant lesion (solid *vs.* cystic),

identify the presence of other nonpalpable nodules within a multinodular goiter, monitor growth of a dominant nodule, recognize thyroiditis, and finally to delineate the presence or absence of suspicious lymph nodes. Thyroid ultrasound is also a useful adjunct to guiding the FNAB procedure.

FNAB is safe and diagnostically reliable and should be routinely performed when any single or dominant thyroid nodule larger than 1 cm has been discovered (193). Successful results with FNAB depend on two important factors: the ability of the practitioner to obtain a valid aspirate for cytological analysis and the skill and expertise of the cytopathologist interpreting the cellular smears. In the particular context of a nodule identified during pregnancy, and because of the potential therapeutic implications, it is highly important that FNAB be carried out and analyzed by experienced teams. However, even in the best possible hands, there is a limit to the capacity of this technique and it should be kept in mind that in a small fraction of FNA results (ideally less than 5%), both false positive and false negative results may occur.

When a valid FNAB has been obtained, subsequent management of nodular thyroid disease depends on the results of the cytological analysis. The majority of thyroid nodules are cytologically benign lesions that do not require surgery. If cytology is suspicious or positive for thyroid cancer, treatment decision-making must take into account several considerations, including the gestational age, the apparent tumor stage, and the personal inclination of the patient. If the result of FNA is consistent with or highly suggestive of papillary, follicular, or medullary carcinoma, surgery is offered in the second trimester but before fetal viability (194). Operation for papillary cancer may be postponed until after delivery if the patient is hesitant to undergo surgery during pregnancy (186, 188, 190, 192, 195, 196).

When the cytology is follicular neoplasm, the risk of malignancy is 10–15% and thyroid surgery can be delayed, if preferred, until a short time after delivery. Most follicular cancers are minimally invasive and well capsulated. In patients who need to be reassured or when there is significant growth of the dominant nodule before mid-gestation, surgery during the second trimester before fetal viability is a valid option. Follicular neoplasms that demonstrate Hurthle cell features (eosinophilic, mitochondrial rich cytoplasm) could represent a Hurthle cell carcinoma, which may be a more aggressive variant of follicular carcinoma. There is controversy about the management of this tumor. It is uncommon, and may be more aggressive, be associated with a higher incidence of metastases, less responsive to iodine treatment, and carry a higher mortality rate (197). Given the possibly more aggressive behavior, the patient should be encouraged to consider surgery in the second trimester if cytology clearly demonstrates Hurthle cell features.

When cytology is indeterminate, one has to decide whether to repeat the FNAB procedure (especially if the first biopsy was not done using ultrasound guidance), or more generally wait until after delivery to complete the work-up of the patient.

It is generally accepted that if a nodule (even when highly suspicious of cancer) is discovered in the third trimester, further work-up and treatment can be delayed until after

delivery (198, 199). The exceptions are for a rapidly growing lesion, an FNA showing anaplastic tumor (fortunately exceedingly rare in this age group), or if waiting until after delivery induces a severe psychological stress to the mother.

5.3. EVIDENCE

5.3.1. Incidence of malignancy in thyroid nodules detected during pregnancy. The prevalence of malignancy in thyroid nodules detected during pregnancy is a source of much discussion in the literature. Rosen (200) presented 28 women referred for thyroid nodules to the University of Toronto School of Medicine and Mount Sinai Hospital Toronto between 1982 and 1985. Thirty-seven percent of the women had an adenoma and 43% had a carcinoma, corresponding to an overall neoplasia rate of 80%. A follow-up study in 66 pregnant women with nodules demonstrated a malignancy rate of 50% (189). Tan *et al.* (199) described 40 pregnant women referred to the Mayo Clinic with thyroid nodules. Sixty-two percent of the women had benign colloid nodules and 15% of nodules were found to be malignant. Marley and Oertel (201) evaluated 57 women referred to George Washington University Medical Center for evaluation of thyroid nodules discovered during pregnancy or the first 3 months postpartum. Thirty percent of the cohort had papillary (21%) or follicular (9%) carcinoma. None of the three studies, however, answers the question of the prevalence of malignancy in thyroid nodules presenting during pregnancy, as they are all limited by referral bias.

In a case control study, McTiernan *et al.* (202) compared women with a diagnosis of thyroid cancer in western Washington State with a random matched control group. Women with one or more pregnancies had a slight, but significant increase in the risk of thyroid carcinoma (relative risk, 1.8; confidence interval, 1.1–3.1). In the prospective study performed by Kung *et al.* (185), all women with a nodule greater than 5 mm underwent fine needle aspiration. Thyroid malignancy was detected in none of the 21 women who were evaluated.

In conclusion, the data, limited as they are, indicate that the malignancy rate is either similar to or possibly greater than that seen in the general population.

5.3.2. Indications for surgery in patients with newly diagnosed thyroid cancer. There is no evidence that pregnancy worsens the prognosis of well-differentiated thyroid cancer found during an existing pregnancy (186, 188, 190, 195, 196) and, therefore, no justification to recommend interruption of pregnancy. In a retrospective cohort by Moosa *et al.* (188), 61 patients with thyroid cancer diagnosed in pregnancy were compared with 528 age-matched, nonpregnant women with a similar distribution of tumor types (>80% papillary) and stage. No differences in outcomes were found with a recurrence rate of 15% in the pregnant women *vs.* 23% in the nonpregnant women. Cancer deaths were 0% in the pregnant women and 1.2% in nonpregnant women. Furthermore, there was no difference in outcome between the patients who had early surgery and those who had delayed surgery, with a median follow-up of 22.4 yr. Thirteen percent of the tumors were stage 1, 69% were stage 2, 16% were stage 3, and 2%

were stage 4. Thirty percent of tumors were diagnosed in the first trimester, 43% in the second, and 28% in the third. Twenty percent of women were operated on in the second trimester and 77% of women underwent thyroidectomy after delivery. The recurrence rate in the women who underwent an operation in pregnancy at a mean of 1.1 months after diagnosis was 14% *vs.* 15% in women who delayed their surgery postpartum at a mean of 16 months after diagnosis.

Yasmeen *et al.* (203) reviewed data from a cancer registry. They compared outcome in 595 women diagnosed with thyroid cancer during pregnancy or within 1 yr after delivery, to an age-matched nonpregnant cohort. They observed no significant difference in outcome during up to 11 yr follow-up. These authors also found no adverse effect of surgery performed during pregnancy on the outcome of pregnancy.

Although there are no data to support pregnancy termination in pregnant women found to have well-differentiated thyroid cancer, there are inadequate data for patients with more advanced disease or who have variants of thyroid cancer associated with a poorer prognosis including medullary, undifferentiated, or anaplastic carcinomas. Surgical treatment should be offered if the patient is less than 22 wk (204), and consideration should be given regarding earlier timing of delivery if the patient is already beyond 23 wk.

If surgical treatment of a thyroid cancer or a nodule suspicious for malignancy is delayed until postpartum, exogenously administered thyroid hormone is recommended to achieve a suppressed but detectable TSH level (189). There are no studies in pregnancy examining the optimal degree of TSH suppression in women discovered to have thyroid cancers or who have highly suspicious nodules. As in the nonpregnant state, the degree of TSH suppression should be dictated by an estimation of the likelihood that the tumor will behave aggressively. However, the free T_4 should be maintained in the upper nonprenant normal range to avoid both maternal and fetal complications. Alternatively, free T_4 can be adjusted to trimester speciifc normal pregnancy ranges if available, or total T_4 to 1.5 times the normal nonpregnant range.

5.3.3. Timing and risks of surgery in pregnancy. If surgery is elected in pregnancy, it is best avoided in the first and third 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 (194). Surgery of any type in the third trimester is associated with a higher incidence of preterm labor. For cancer found early in pregnancy, surgery during the second trimester before fetal viability (<22 wk) appears safe for the patient and the fetus (186, 189, 198, 200). Fetal loss has been reported only in association with extensive neck exploration (205). Most recent reports note no fetal complications using contemporary monitoring techniques (186, 198). The decision to operate during pregnancy should take into consideration the patient's attitude about forestalling treatment until postpartum as well as concerns about fetal risk.

5.3.4. Monitoring and management of patients with previously diagnosed thyroid cancer. There are no data that subsequent pregnancy increases the risk for thyroid cancer recurrence.

Several series have examined the natural history of cancer recurrence in women who became pregnant after receiving treatment for thyroid cancer. There was no evidence that thyroid cancer was influenced by the pregnancy. Rosvoll (206) reported that 38 women who were disease free 2–15 yr before pregnancy had no recurrence of their thyroid cancer either during or after pregnancy. Similarly, Hill *et al.* (195) compared 70 women with pregnancies after their diagnosis of thyroid cancer to 109 women with thyroid cancer who had no pregnancies following the diagnosis. The recurrence rate between the two groups of women was similar, leading the authors to conclude that pregnancy subsequent to the diagnosis of thyroid carcinoma seemed to have no effect on the course of the disease.

Women who were receiving suppressive dosage of exogenous thyroxine before pregnancy for thyroid cancer may continue to do so as long as the free T_4 or total T_4 does not rise out of the normal range for pregnancy. Although there are no outcome data in pregnancy, it appears reasonable that the same guidelines outside of pregnancy be used to determine the degree of TSH suppression according to whether the woman has evidence of persistent disease (<0.1 mU/liter) or appears clinically free of disease (0.1–0.5 mU/liter) (207). In women who have received RAI ablation, monitoring for evidence of recurrence using TG may be useful. Inappropriately elevated levels indicate concern for residual disease and need for careful palpation and neck ultrasound (189).

5.3.5. Implications of 131-I ablative therapy on breast-feeding and subsequent pregnancy. Prior treatment with 131-I does not appear to affect subsequent pregnancy outcome. Several series (195, 196, 208–210) have demonstrated that prior RAI administration did not adversely affect congenital malformations, successful delivery, mode of delivery, live births, or 1-yr neonatal mortality. In one study, which collected information on pregnancies from 1044 unselected women treated for thyroid cancer, the incidence of miscarriage was slightly increased in women treated with 131-I during the year preceding conception. This was thought to be secondary to inadequate control of thyroid hormone status following thyroidectomy (196). In this study, there was no evidence that exposure to RAI affected stillbirths, low birth weights, prematurity, congenital malformations, or the rate of nonthyroidal malignancy in the children. Furthermore, in a series of 78 live births to women with prior therapy, information on children was available at a mean of 8 yr old and there was no indication of abnormal development (209). A higher ablative dose (>80 mCi) and a shorter interval between RAI and conception (<1 yr), did not significantly affect pregnancy outcome.

Nursing women should not be offered 131-I therapy because of concentration of isotope in the lactating breast and transfer of the isotope to the infant. It has also been recommended that lactation be discontinued for 1–2 months before 131-I treatment to avoid excess breast exposure, but the minimal time for discontinuation is several days (211). Conception should occur after remission of thyroid cancer has been documented and stability of thyroid function has been achieved, which often requires 1 yr after 131-I ablative treatment (189, 196, 208–210).

5.4. RECOMMENDATIONS

5.4.1. Fine needle aspiration (FNA) cytology should be performed for single or dominant thyroid nodules larger than 1 cm discovered in pregnancy. Ultrasound guided FNA may have an advantage for minimizing inadequate sampling. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕⊕○) (185, 187, 188, 190).

5.4.2. When nodules are discovered in the first or early second trimester to be malignant on cytopathological analysis or exhibit rapid growth, pregnancy should not be interrupted but surgery should be offered in the second trimester, before fetal viability. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease, 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 surgical treatment soon after delivery is unlikely to change prognosis. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○) (187, 188, 190, 192).

5.4.3. It is appropriate to administer thyroid hormone to achieve a suppressed but detectable TSH in pregnant women with a previously treated thyroid cancer, or an FNA positive for or suspicious for cancer, and those who elect to delay surgical treatment until postpartum. High-risk patients may benefit more from a greater degree of TSH suppression compared with low-risk patients. The free T_4 or total T_4 levels should ideally not be increased above the normal range for pregnancy. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (189).

5.5.4. RAI with 131-I should not be given to women who are breast-feeding. The USPSTF recommendation level is B; evidence is fair. 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. The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○) (186, 196, 209).

5.5. REMARKS

None.

5.6. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

Choe W, McDougall IR 1994 Thyroid cancer in pregnant women: diagnosis and therapeutic management. Thyroid 4:433–435

Retrospective analysis of 263 pregnancies after treatment of thyroid cancer at Queen Elizabeth Hospital in Hong Kong. In 153 pregnancies, scanning or ablative doses of 131-I had been used to manage thyroid cancer. Subsequent pregnancy outcomes including the rate of successful deliveries, live birth demographics, congenital malformations, and first year neonatal mortality did not demonstrate any effect of prior 131-I use. There was no abnormal development noted in 78

reported offspring at age 1 month to 31 yr (mean 8 yr) whose mothers received ablative doses of 131-I. However, there was a slightly higher incidence of preterm delivery in those with a history of 131-I treatment.

Herzon FS, Morris DM, Segal MN, Rauch G, Parnell T 1994 Coexistent thyroid cancer and pregnancy. Arch Otolaryngol Head Neck Surg 120:1191–1193

Retrospective analysis of thyroid cancer cases obtained from the New Mexico Tumor Registry. No statistically significant survival rates were observed in the pregnant women *vs.* nonpregnant women of similar age and with comparable thyroid cancers.

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

Prospective study of 221 healthy southern Chinese women who received thyroid ultrasound during pregnancy and postpartum. Thyroid nodules of at least 2 mm were detected in 15.3% of the women and the volume slightly, but statistically significantly, increased. New nodules were detected in 11.3% as pregnancy advanced. FNA was done on 21 nodules larger than 5 mm and no thyroid malignancy was noted.

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

Prospective collected information on 1355 patients with papillary or follicular cancer treated in the United States Air Force or Ohio Sate University with a median follow-up of 15.7 yr. The likelihood of cancer death was increased by age 40 yr or older, tumor size 1.5 cm or larger, local tumor invasion, regional lymph-node metastases, and delay in therapy 12 months or more and reduced by surgery more extensive than lobectomy and 131-I plus thyroid hormone therapy.

Moosa M, Mazzaferri EL 1997 Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab 82:2862–2866

Prospectively gathered information from the United States Air Force Tumor Registry in which thyroid tumor type and outcome of 61 pregnant women were compared with 203 nonpregnant women with thyroid cancer. No significant differences were found in regards to tumor cell type, tumor size or local invasion. Specifically, 87% of pregnant women had papillary carcinoma, with a mean tumor size of 2.1 cm and local invasion rate of 13%. Nonpregnant women had nearly identical values of 81%, 2.0 cm, and 12%, respectively. Similarly, cancer recurrence and death secondary to thyroid malignancy were not significantly different in the groups. Furthermore, there was no difference in outcome in the pregnant patients who had surgery during pregnancy or those who had surgery delayed until postpartum with a median follow-up of 22.4 yr in the cohort.

Rosen IB, Korman M, Walfish PG 1997 Thyroid nodular disease in pregnancy: current diagnosis and management. Clin Obstet Gynecol 40:81–89

Review of the thyroid nodule and cancer in pregnancy experience at Mount Sinai Hospital in Toronto and University of Toronto School of Medicine in addition to a review of the literature at other centers.

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

Report of a collaborative study by the nuclear medicine institutes at Pisa, Italy and Gustave-Roussy, France which obtained interview information on 1044 unselected female patients treated for thyroid cancer. The incidence of miscarriages was 13% before any treatment and increased slightly after surgery for thyroid cancer, both before and after 131-I, but did not vary with the cumulative 131-I dose. Miscarriages were more frequent in women treated with 131-I during the year preceding the conception, thought to be due to inadequate control of the thyroidal hormonal status. There was no increase in stillbirth, preterm birth, low birth weight, or congenital malformations after 131-I treatment.

Vini L, Hyer S, Pratt B, Harmer C 1999 Management of differentiated thyroid cancer diagnosed during pregnancy. Eur J Endocrinol 140:404–406

Retrospective analysis of 9 women in the UK diagnosed with well differentiated thyroid cancer during pregnancy. One patient underwent subtotal thyroidectomy during the second trimester and the remaining eight were operated on within 3–10 months after delivery. Women were followed for a median of 14 yr. Eight patients were disease free including one woman who relapsed locally requiring further surgery. One patient developed bone metastases and died 7 yr after presentation after delaying her treatment due to an intervening pregnancy.

SECTION 6. IODINE NUTRITION DURING PREGNANCY

6.2. BACKGROUND

Iodine nutrition in women before pregnancy. In 2001, the World Health Organization officially endorsed recommendations made by international organizations such as the ICCIDD (International Council for Control of Iodine Deficiency Disorders) and UNICEF (United Nations Children's Fund) to eliminate ID disorders, on the basis that ID present at critical stages during pregnancy and early childhood resulted in impaired development of the brain and consequently in impaired mental function (212). The recommended nutrient intake (RNI) for iodine in adults and children above the age of 12 yr is 150 μg/d. Although a variety of methods exists for the correction of ID, the most commonly applied method is universal salt iodization (USI), *i.e.* the addition of suitable amounts of potassium iodide (or iodate) to all salt for human and livestock consumption.

Iodine nutrition in women during pregnancy. During pregnancy, several physiological changes take place in maternal thyroid economy which, together, lead to an increase in thyroid

hormone production of approximately 50% above the pre-conception baseline hormone production. To achieve the necessary increment in thyroid hormone production, the iodine intake needs to be increased during early pregnancy (49, 213, 214). During pregnancy serum total T_4 and T_3 values increase following the rapid increase in serum TBG concentrations that results from sustained estrogen stimulation (77, 215). Early in pregnancy, there is an increase in renal glomerular filtration leading to increased plasma iodide clearance.

It was previously—and wrongly—considered that the thyroid gland was adapting physiologically to the pregnant state without significant changes in healthy women (216). Today, this view has been completely modified as it is now accepted that the production rate of thyroid hormone increases by approximately 50% during pregnancy. The rapid and marked increase in the extrathyroidal pool of thyroxine explains the need to adapt thyroid hormone production during the first half of gestation to reach a new steady-state and maintain normal free T_4 concentrations (49).

In women with iodine sufficiency, there is little impact of the obligatory increased renal iodine losses because the intrathyroidal iodine stores are plentiful at conception and remain unaltered throughout gestation (217). The situation is markedly different in pregnant women who have a restricted, or deficient, iodine intake, and this is clearly shown by the decrease in UIE (urinary iodine excretion) levels in such conditions (214).

Dietary ID occurring during pregnancy (even when considered mild or moderate) leads to maternal hypothyroxinemia, enhanced thyroidal stimulation via the pituitary (TSH) feedback mechanisms, and ultimately goiter formation in mother and fetus (49, 218–221). When such women are given iodine supplements started early during gestation, goiter formation can be prevented (222).

6.3. EVIDENCE

Iodide intake during pregnancy. Women should have an adequate iodine intake, corresponding to 150 μg/d to ensure that intrathyroidal iodine stores are replenished before they become pregnant. Several population studies, carried out in the 1990s, have shown that when women with an iodine intake less than 100 μg/d become pregnant, the pregnancies are frequently associated with thyroid function abnormalities (mainly maternal hypothyroxinemia) resulting in excessive thyroidal stimulation and goiter formation in both the mother and offspring (77, 221, 223–228).

The RNI for iodine during pregnancy has been re-evaluated in 2005 by an international expert committee under the auspices of the World Health Organization (229). The consensus reached was that the RNI for iodine during pregnancy and breast-feeding should range between 200 and 300 μg/d, with an average of 250 μg/d. Furthermore, several pregnancy population studies, carried out between 1981 and 2002, have shown that iodine supplementation maintained normal thyroid function, thus avoiding maternal hypothyroxinemia and preventing maternal and neonatal goitrogenesis (222, 230–236).

Upper limit of safety for iodine intake in pregnancy. Excessive levels of iodine intake may potentially cause more disease. Furthermore, individuals must be identified who may have side effects from excessive iodine intake, such as patients with known or underlying autoimmune thyroid disorders or autonomous thyroid tissue (237). Because there is no strong evidence to define clearly "how much more iodine may become too much iodine," the most reasonable recommendation is to indicate that there is no proven further benefit in providing pregnant women with more than twice the daily RNI.

Iodine nutrition during breast-feeding. During breast-feeding, thyroid hormone production and UIE return to normal, but iodine is efficiently concentrated by the mammary gland. Because breast milk provides approximately 100 μg of iodine/d to the infant, it is recommended that the breast-feeding mother should continue to take 250 μg/d of iodine.

Implementation of iodine nutrition fortification during pregnancy. The overall consideration is that the sooner the iodine fortification is implemented (ideally, no later than in the first trimester), the better is the resulting adaptation of thyroid function to the pregnant state. To implement the RNI for iodine during pregnancy, the natural iodine intake level in a population must be taken into account and, therefore, multiple tailored means must be used to reach the RNI for iodine. Several epidemiological situations must be distinguished. In countries with a longstanding and well-established USI program, pregnancies are not at risk of having ID. Therefore, no systematic dietary fortification needs to be organized in these populations. It can, however, be recommended individually to pregnant women to use multivitamin tablets prepared specifically for the needs of pregnancy and containing iodine supplements, because it is known that even in such apparently satisfactory iodine intake conditions a fraction of pregnant women may still have an insufficient dietary iodine intake (238). Women should be advised to check their vitamin preparation to make certain that the correct amount of iodine is included. In countries without an efficient USI program, complementary approaches are required to reach the RNI for iodine. Such approaches include the use of oral iodine supplements in the form of potassium iodide (100–200 μg/d) or the inclusion of KI (125–150 μg/d) in multivitamin tablets specifically designed for pregnancy. Finally in areas with no accessible USI program and difficult socioeconomic conditions generally, it is recommended to administer orally iodized oil orally as early during gestation as possible. Four hundred milligrams (400 mg) of iodine given orally will cover thyroidal needs for about a 1-yr period (231).

Monitoring the adequacy of iodine intake. The best single parameter to evaluate the adequacy of iodine nutrition in a population is provided by UIE levels. In conditions with an adequate iodine intake during pregnancy, the UIE should ideally range between 150 and 250 μg/d (or 100–200 μg/liter, based on an average 1.5 liter of daily urine output) (239). However, although UIE is highly useful for public health estimations of iodine intake levels in populations, UIE alone is not a valid diagnostic criterion in individuals. For example, a recent national health study in the United States (NHANES

III survey) has indicated that despite a median iodine intake level of approximately 150 μg/d in the entire population, 5–20% of women in the childbearing age and 5–10% of pregnant women may still have an insufficient iodine intake (238). Even though no public health measure is required to correct ID in this population, individual counseling should suggest an increase in iodine intake during pregnancy.

To assess the adequacy of the iodine nutrition level in an individual, the best single parameter would be to estimate the amount of stable iodine stored within the thyroid gland, corresponding to approximately 10–20 mg of iodine in iodine-sufficient conditions. However, this parameter is not measurable in practice. Therefore, in a given pregnant woman, the best surrogate is to evaluate those thyroid parameters that have been shown to be sensitively altered when a pregnancy takes place in iodine-deficient women. Iodine restriction during pregnancy results in a significant lowering in serum free T_4 as well as a rise in TSH, a progressive increase in serum TG, an elevation of the total molar T_3/T_4 ratio, and finally an increase in thyroid volume (TV) that may lead to goiter formation in both the mother and fetus.

6.4. RECOMMENDATIONS

6.4.1. Women in the childbearing age should have an average iodine intake of 150 μg/d. During pregnancy and breast-feeding, women should increase their daily iodine intake to 250 μg on average. The USPSTF recommendation level A; evidence is good (GRADE 1|⊕⊕⊕○) (219, 220, 229, 238).

6.4.2. Iodine intake during pregnancy and breast-feeding should not exceed twice the daily RNI for iodine, *i.e.* 500 μg iodine/d. The USPSTF recommendation level is I; evidence is poor (⊕○○○) (219, 220, 229, 238).

6.4.3. To assess the adequacy of the iodine intake during pregnancy in a population, urinary iodine concentration (UIC) should be measured in a representative cohort of the population. UIC should ideally range between 150 and 250 μg/liter. The USPSTF recommendation level A; evidence is good (GRADE 1|⊕⊕⊕⊕) (239).

6.4.4. To reach the daily RNI 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. The USPSTF recommendation level is A; evidence is good (GRADE 1|⊕⊕⊕⊕) (222, 231–233, 235).

6.5. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

Chaouki ML, Benmiloud M 1994 Prevention of iodine deficiency disorders by oral administration of lipiodol during pregnancy. Eur J Endocrinol 130:547–551

Prospective study on iodine prophylaxis in an area with severe ID in Algeria: Lipiodol (0.5 ml by oral administration) given once to three groups of pregnant women, compared with a group of untreated women serving as controls. Group A was treated 1–3 months before conception; group B was treated during the first month; group C was treated during the third month. In all three treated groups, mothers and newborns remained euthyroid and there was no visible neonatal goiter. The rates of prematurity (11% *vs.* 14%), stillbirths (9% *vs.* 20%) and abortions (0% *vs.* 19%) were significantly reduced in treated mothers, compared with the controls. No difference was observed with respect to timing of the iodoprophylaxis. Conclusion: oral administration of Lipiodol before or during the first trimester of pregnancy normalizes thyroid function in mothers and their newborn babies.

Delange F 2004 Optimal iodine nutrition during pregnancy, lactation and the neonatal period. Int J Endocrinol Metab 2:1–12

Review article analyzing data from literature on dietary iodine requirements during pregnancy, lactation and the neonatal period. Conclusions: 1) iodine requirements are 250–300 μg/d during pregnancy, with similar daily amounts during lactation, and 90 μg/d for infants in neonatal period; 2) median UIE levels indicating optimal iodine nutrition should be in the range of 150–230 μg/liter.

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Pregnancy is associated with profound alterations in the thyroidal economy, resulting from a complex combination of factors specific to the pregnant state. Together, these factors concur to stimulate excessively the maternal thyroid machinery. When gestation takes place in iodine-deficient conditions, increased thyroidal stimulation induces, in turn, a sequence of events leading from physiological adaptation of the thyroidal economy observed in healthy iodine-sufficient pregnant women to pathological alterations affecting both thyroid function and the anatomical integrity of the thyroid gland.

Glinoer D, De Nayer P, Delange F, Lemone M, Toppet V, Spehl M, Grun 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

One hundred eighty euthyroid healthy women were randomized in a double-blind prospective protocol into three groups and treated until term with placebo, 100 μg KI/d, or 100 μg iodide + 100 μg thyroxine/d. In placebo-treated women, indices of excessive thyroidal stimulation worsened as gestation progressed whereas in both groups receiving active treatment, thyroid function was markedly improved. In placebo-treated women, TV increased by a mean of 30%, with 16% of the women developing a gestational goiter. Moreover, 10% of newborns of these mothers had significantly enlarged TVs at birth. The goitrogenic stimulus associated with pregnancy in iodine-deficient conditions was strikingly minimized in the KI-treated group and almost completely suppressed in the KI + T_4-treated group. Furthermore, neonatal TV remained normal in all newborns of mothers who received active treatment. Conclusions: first study to clearly show (using a randomized prospective double-blind trial) the benefits of iodine prophylaxis during

pregnancy in conditions with mild/moderate ID to avoid hypothyroxinemia and glandular stimulation leading to goiter formation in both mothers and newborns.

Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, Braverman LE, Pino S, Miller DT, Garbe PL, DeLozier DM, Jackson RJ 1998 Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from national health and nutrition examination surveys I and III (1971–1974 and 1988–1994). J Clin Endocrinol Metab 83:3401–3408

The National Health & Nutrition Examination Surveys (NHANES I; 1971–1974) and NHANES III (1988–1994) measured UICs as an indicator of the adequacy of iodine intake in the U.S. population. Median UIC from NHANES III survey indicated adequate iodine intake for the overall U.S. population, but showed a 50% decrease between 1971–1974 and 1988–1994 (from 320 to 145 μg/liter). Low UIC values (<50 μg/liter) were found in 12% of the population in NHANES III survey. UIC values less than 50 μg/liter were found in 6.7% of pregnant women and in 14.9% of women in the child-bearing age. Conclusion: the 1988–1994 findings, although not indicative of ID in the overall U.S. population, define a trend that must be monitored closely, especially in at-risk target groups such as the young females.

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

TV and UIE investigated in women receiving 300 μg KI/d and women without iodine prophylaxis during pregnancy. In women with iodine supplementation, UIE was significantly increased at delivery in both the mothers and newborns. TVs in newborns of mothers who received iodine prophylaxis were significantly smaller compared with controls, whereas no difference was observed in TVs of mothers, between treated and control groups. A plausible explanation for the absence of beneficial effect of iodine prophylaxis on maternal TV is the fact that the study was undertaken in Berlin (an area known to have been moderately to severely iodine deficient), as indicated by the presence of a preexisting goiter in almost one half of the women included in present work. Conclusion: 1) iodine supplementation during pregnancy in an area with moderate/severe ID resulted in a lower size of neonatal TV; 2) iodine supplementation was not accompanied by an increase in the frequency of thyroid autoantibodies.

Nohr, 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

Study in Denmark in an area with mild to moderate ID: 49 pregnant women with a daily supplement of 150 μg of iodine, compared with 95 pregnant women without iodine supplements. In iodine-supplemented mothers, serum TSH decreased by 8%, whereas in their newborns (in cord blood) there was an opposite effect, with higher neonatal serum TSH by 27% in the supplemented group. Conclusion: the fetal

thyroid gland (at least in areas of mild ID) is sensitive to the inhibitory effect of iodine.

Pedersen KM, Laurberg P, Iversen E, Knudsen PR, Gregersen HE, Rasmussen OS, Larsen KR, Eriksen GM, Johannesen PL 1993 Amelioration of some pregnancy-associated variations in thyroid function induced by iodine supplementation. J Clin Endocrinol Metab 77:1078–1083

Study in an area in Denmark (Aalborg) with mild-moderate ID. Pregnant women were randomized to receive 200 μg iodine/d (*vs.* no treatment) from wk 17–18 of pregnancy until after delivery. In women without iodine supplementation, pregnancy was associated with significant increases in serum TSH, TG, and TV. In contrast, these variations were significantly ameliorated in the group of women who received iodine supplements during gestation.

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. Amer J Obstet Gynecol 164:482–485

Prospective evaluation of TV by ultrasound in pregnant women in an area in Italy with moderate ID. Iodized salt (120–180 μg of iodine/d) was administered to group A women; untreated group B women served as controls. In the third trimester of gestation, mean UIE level was significantly higher in the treated group than in controls ($P < 0.01$). TV did not differ between both groups at the onset of pregnancy, whereas at the end of pregnancy, TV remained unchanged in group A, while increasing significantly in untreated women ($P < 0.0001$). Conclusions: moderate ID leads to thyroidal stimulation and increased TV during pregnancy and iodoprophylaxis prevents maternal goitrogenesis.

World Health Organization, Technical consultation of experts in Geneva in January 2005. The prevention and control of ID in pregnant and lactating women and in children under two years: recommendations of a WHO Technical Consultation. Public Health Nutr, in press, 2007

The RNI for iodine in adults and children above the age of 12 yr is 150 μg/d. The most commonly method applied for correcting ID is USI, *i.e.* the addition of suitable amounts of potassium iodide (or iodate) to all salt for human and livestock consumption. To achieve the necessary increment in thyroid hormone production associated with pregnancy, the iodine intake needs to be increased. RNI for iodine during pregnancy and breast-feeding should range between 200 and 300 μg/d, with an average intake of 250 μg of iodine/d.

SECTION 7. POSTPARTUM THYROIDITIS

7.2. BACKGROUND

PPT is the occurrence of hyperthyroidism, hypothyroidism, and/or hyperthyroidism followed by hypothyroidism in the first year postpartum in women without overt thyroid disease before pregnancy. It is believed caused by an autoimmunity-induced discharge of preformed hormone from the thyroid, and is characterized by a near 0% RAI uptake

during the active process. PPT occurs almost exclusively in women who are thyroid antibody positive.

7.3. EVIDENCE

7.3.1. Prevalence of PPT.

7.3.1.1. Prevalence in unselected populations. The reported prevalence of PPT varies globally from as low as 1.1% in Thailand to as high as 21.1% in Canada (68, 240). 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% (241). The prevalence varies internationally with an estimated prevalence of 5.5–6.5% in Japan, 3.3–8.7% in Europe, 5–16.7% in the UK, 10.3% in Australia, and 14.6% in Brazil. It also varies within the United States with a prevalence as low as 3.3% in Washington, DC to 8.8% in the New York metropolitan area. The prevalence reported in various studies is influenced by the timing of the initial screen and whether scintigraphy was performed. Some women diagnosed with PPT likely have preexisting Hashimoto's or postpartum Graves' disease. Incidence is also affected by genetic influences (240), iodine intake (242), and smoking (243).

7.3.1.2. 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% (244). In accord with this, the incidence of PPT in women with type 1 DM is higher than in an unselected population and ranges from 18–25% (245, 246). Gerstein assessed 51 patients with type 1 DM in Ontario at the first postpartum week and again at 3–6 months after delivery. Forty patients completed the study and nine were diagnosed with PPT (246). In a second study in New York, 41 women with type 1 DM were recruited at their first prenatal visit and followed prospectively with thyroid function tests at 6 wk and at 3, 6, 9, and 12 months postpartum. Of the 28 women who completed the study, 25% developed PPT (245).

7.3.2. 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 (and therefore before and during pregnancy) (247). Among these, TPO-Ab is the most useful marker for the prediction of postpartum thyroid dysfunction (248). The seminal report, published in 1982, discovered an incidence rate of PPT of 5.5% (248). The investigators found that 89.1% of PPT patients were thyroid antibody-positive, and 40.3% of subjects with thyroid antibodies developed PPT (248). By contrast, only 0.6% of antibody-negative subjects had PPT, thus establishing the strong association of thyroid antibody positivity and PPT. In women with TPO-Ab, lymphocytic infiltration into the thyroid is always observed, and therefore these subjects have "subclinical autoimmune thyroiditis" (249), which exacerbates after delivery. Forty to 60% of women with positive TPO-Ab in early pregnancy develop postpartum thyroid dysfunction (250, 251). The risk to develop postpartum thyroid dysfunction in the TPO-Ab-negative subjects is estimated to be one tenth to one hundredth of that in TPO-Ab-

positive women (247). The majority of mothers with high titers of antibody develop postpartum thyroid dysfunction (252–256).

7.3.3. Symptoms of women with PPT.

7.3.3.1. Hyperthyroid symptoms. The hyperthyroid phase of PPT occurs between 1 and 6 months postpartum (most commonly at 3 months) and usually lasts only 1–2 months. Patients with prior Graves' disease may also develop PPT, but the strength of the association is uncertain (257, 258). It is important to differentiate between the thyrotoxic phase of PPT and Graves' disease presenting *de novo* in the postpartum period. From an epidemiological perspective, the thyrotoxic phase of PPT is 20 times more common than postpartum Graves' disease. Symptoms during the thyrotoxic phase of PPT tend to be milder than during thyrotoxicosis due to Graves' disease. Furthermore, 95% of women with Graves' disease are TSH receptor antibody-positive and may also present with a thyroid bruit and exophthalmos. In contrast to Graves' disease, PPT is characterized by a near 0% RAI uptake.

Twenty to thirty percent of patients who develop PPT have only hyperthyroid symptoms. Fatigue, palpitations, weight loss, heat intolerance, nervousness, anxiety, and irritability are more prevalent in women with PPT than in euthyroid women (248, 257, 259). The frequency of asymptomatic hyperthyroidism among patients with PPT is approximately 30% (68).

7.3.3.2. Hypothyroid symptoms. The hypothyroid phase of PPT usually occurs between 3 and 8 months (most commonly at 6 months) and is due to loss of thyrocytes by immune destructive mechanisms. 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 (241, 260). Hypothyroidism tends to happen earlier when preceded by thyrotoxicosis than when it occurs alone (240). 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 (241, 247, 259, 261).

7.3.4. Association of PPT with postpartum depression (PPD).
The incidence of PPD in nonselected populations using DSM-III-R criteria appears to be approximately 10% (262, 263). 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. The data are conflicting.

The rationale behind a possible association between positive PPD and PPT is that hypothyroidism is associated with depression outside of the postpartum period and that hypothyroidism appears to decrease 5-hydroxytrytamine neurotransmission which reverses with thyroid hormone replacement (264). The pathophysiological evidence between the association of thyroid antibodies and depression is less clear. However, it is speculated that cytokines released dur-

ing thyroid autoimmune reactions, such as IL-1 and IL-6, may interact with central neurotransmission, thereby initiating depression (265).

Three studies specifically evaluated the association of thyroid antibodies and PPD, independent of thyroid dysfunction. Two of them found a statistically significant association and one did not. Harris (266) followed 110 thyroid antibody-positive and 132 antibody-negative women from Wales from 6 to 28 wk postpartum and performed a double-blind comparison of their psychiatric status using a number of different depression and anxiety scales. He found that 47% of antibody-positive (cases) and 32% of antibody-negative women (controls) were depressed by Research Diagnostic Criteria, regardless of thyroid dysfunction, and the difference was statistically significant. Kuijpens (267) prospectively followed 310 unselected women from The Netherlands and obtained TPO-Ab antepartum and performed thyroid function tests antepartum and at five time points between 4 and 36 wk postpartum. After excluding women who were found to be depressed antepartum, he found that the presence of TPO-Ab early in pregnancy was associated with depression postpartum only at 4 and 12 wk, with an OR of 2.8 (1.7–4.5). However, in another study done in The Netherlands, Pop *et al.* (268) investigated the presence of antimicrosomal antibodies present at 32 wk gestation in a random population of 293 women. The incidence of PPD was also assessed using Research Diagnostic Criteria. Compared with antibody-negative women, those with positive antibodies had an RR that was 1.7-fold higher for the development of PPD, which was not statistically significant.

In 1991 Pop *et al.* (269) evaluated 293 women during pregnancy and postpartum for PPT and PPD. Thirty-eight percent (8/21) of the women with PPT were also depressed compared with a euthyroid control group which had an incidence of depression of 9.5% ($P = 0.02$). Hayslip *et al.* (270) followed 51 women in Washington, DC who were antimicrosomal antibody-positive for at least 6 months postpartum. Thirty-four (67%) women developed postpartum thyroid dysfunction, and impaired concentration, carelessness, and depression were statistically more common in the patients with hypothyroidism than in the antibody-positive patients without hypothyroidism. Lucas *et al.* (271) followed 441 unselected women in Spain for the occurrence of PPD and examined the association between women with postpartum thyroid dysfunction *vs.* women who did not, irrespective of antibody status. In this negative study, they found a low incidence of PPD (7.8% of Beck Depression Inventory scores suggestive and 1.7% definitive), but no association with thyroid dysfunction.

The largest trial—one that used a double-blind clinical assessment to examine the prevalence of PPD in women with positive thyroid antibodies alone, those with thyroid dysfunction, and those without any evidence of either thyroid antibodies or thyroid dysfunction—was negative (257). A total of 749 Caucasian women from Australia received thyroid function tests and TPO-Ab assays at approximately 6 months postpartum and were mailed a self-administered questionnaire for depression. Women scoring above a predetermined value were evaluated by a single interviewer using a battery of depression scales. Both the patient and

interviewer were blinded regarding the biochemical thyroid tests. The prevalence of postpartum thyroid dysfunction was 11.5% overall, with 70% of women demonstrating either a high TSH or low free T_4 and 30% having a suppressed TSH. TPO-Ab were present in 64% of the group with thyroid dysfunction *vs.* 5% with normal thyroid function. The 6-month prevalence rate of depression was 9.4% overall, and there was no relationship between PPD and either thyroid dysfunction or antibody status.

In conclusion, studies have not revealed a consistent association between PPD and either PPT or the presence of thyroid antibody positivity in euthyroid women postpartum. Nevertheless, the presence of a positive association in a number of studies leads to speculation that an association does exist in a subset of women which, to date, has not been identified.

7.3.5. The optimal treatment for PPT. There have been no controlled studies evaluating the optimal treatment for PPT. Stuckey *et al.* (272) reported the results of a questionnaire distributed to endocrinologists and to general practitioners regarding the threshold TSH level at which they would recommend institution of thyroxine therapy. In both groups, a majority used a TSH level between 10 and 20. Stagnaro-Green *et al.* (68) developed an algorithm for therapy in PPT. In the hyperthyroid phase of PPT, intervention with propranolol was recommended for women with symptoms of palpitations, fatigue, heat intolerance, and/or nervousness. The dose of propranolol should be titrated to achieve symptomatic relief. The duration of therapy typically does not exceed 2 months. 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 do not necessarily require intervention and should, if untreated, be re-evaluated in 4–8 wk. Women with a TSH between 4 and 10 who are either symptomatic or attempting to become pregnant should be treated with thyroxine. Finally, all women with a TSH that exceeds 10 should be treated with thyroxine.

7.3.6. 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 following recovery from hypothyroidism, abnormalities in ultrasonography and/or iodide perchlorate discharge tests persist (273, 274), 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 (259, 275–278). Consequently, long-term follow-up is necessary, although a model predicting who will develop permanent hypothyroidism has not been elucidated.

Tachi *et al.* (278), who followed 44 Japanese women with a history of PPT for a mean interval after delivery of 8.7 yr, reported that 29% developed permanent hypothyroidism. High titers of TG-Ab and HLA-DRw9 and/or B51 genotype were risk factors for permanent hypothyroidism. Othman *et*

al. (276) followed 43 patients with PPT for 2–4 yr and found permanent hypothyroidism in 23%. They found high titers of microsomal antibodies and the severity of the initial hypothyroid phase were risk factors for the late development of permanent hypothyroidism. Premawardhana *et al.* (277) followed 48 TPO-positive women who had PPT and examined them at 77–81 months. Subclinical or clinical hypothyroidism developed in 46%. The authors reported that high TPO-Ab titers and thyroid hypo-echogenicity were predictors of permanent hypothyroidism. Azizi (275) withdrew thyroxine in 172 women who were treated for postpartum hypothyroidism for an average of 23 months. After withdrawal of thyroxine, 59% of women who initially had subclinical postpartum hypothyroidism and 64% of women who presented with overt postpartum hypothyroidism became hypothyroid.

7.3.7. Selenium supplementation in women at risk for PPT. Negro *et al.* (279) recently published the results of a prospective, randomized placebo controlled study. A cohort of euthyroid thyroid antibody-positive women in the first trimester of pregnancy were administered selenium on a daily basis (n = 85) and a control group of thyroid antibody-positive women were given placebo (n = 84). The occurrence of PPT was significantly less in the women administered selenium than in women given placebo (28.6% *vs.* 48.6%, $P < 0.01$).

7.4 RECOMMENDATIONS

7.4.1. There are insufficient data to recommend screening of all women for PPT. The USPSTF recommendation level is I; evidence is poor ($\oplus\bigcirc\bigcirc\bigcirc$) (68, 240).

7.4.2. Women known to be TPO-Ab-positive should have a TSH performed at 3 and 6 months postpartum. The USPSTF recommendation level is A; evidence is good (GRADE 1|$\oplus\oplus\oplus\bigcirc$) (68, 251).

7.4.3. The prevalence of PPT in women with type 1 DM is 3-fold greater than in the general population. Postpartum screening (TSH determination) is recommended for women with type 1 DM at 3 and 6 months postpartum. The USPSTF recommendation level is B; evidence is fair (GRADE 1|$\oplus\oplus\bigcirc\bigcirc$) (244–246).

7.4.4. Women with a history of PPT have a markedly increased risk of developing permanent primary hypothyroidism in the 5- to 10-yr period following the episode of PPT. An annual TSH level should be performed in these women. The USPSTF recommendation level is A; evidence is good (GRADE 1|$\oplus\oplus\oplus\bigcirc$) (275–278).

7.4.5. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 μU/ml and who are not planning a subsequent pregnancy do not necessarily require intervention, but should, if untreated, be remonitored in 4–8 wk. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine. The USPSTF recommendation level is B; evidence is fair (GRADE 1|$\oplus\oplus\bigcirc\bigcirc$) (68).

7.4.6. 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). The USPSTF recommendation level is I; evidence is poor (258, 260, 262, 263, 266, 268). However, as hypothyroidism is a potentially reversible cause of depression, women with PPD should be screened for hypothyroidism and appropriately treated. The USPSTF recommendation level is B; evidence is fair (GRADE 2|$\oplus\oplus\bigcirc\bigcirc$) (264).

7.5. REMARKS

None.

7.6. BIBLIOGRAPHY—ITEMS RELATED TO RECOMMENDATIONS

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
  The manuscript by Alvarez-Marfany *et al.* determined the incidence of PPT in 28 pregnant women with type 1 DM in the New York metropolitan area. Twenty-five percent of the women developed PPT. In a prior study, women without DM in the New York metropolitan area had an incidence of PPT of 8.8%.

Azizi F 2005 The occurrence of permanent thyroid failure in patients with subclinical postpartum thyroiditis. Eur J Endocrinol 153:367–371
  Azizi evaluated 172 women who had a history of PPT for the development of permanent thyroid dysfunction. On average, women were assessed 23 months following the episode of PPT. Fifty-nine percent of women who had SCH at the time of PPT, and 64% of women who had OH at the time of PPT were found to have developed permanent thyroid failure.

Gerstein HC 1993 Incidence of postpartum thyroid dysfunction in patients with type 1 diabetes mellitus. Ann Intern Med 118:419–423
  Gerstein performed a prospective study of 40 women with type I DM. Women were screened for thyroid dysfunction at 1 wk postpartum, and subsequently at 3 and 6 months following delivery. Twenty-five percent of the women developed postpartum thyroid dysfunction.

Kuijpens 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
  Kuijpens *et al.* followed a cohort of women from 12 wk gestation until 36 wk postpartum. Thyroid antibody determinations and thyroid function testing were performed at regular intervals. TPO-Ab positivity in early pregnancy was associated with PPD.

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

The article by Muller *et al.* is a comprehensive review of PPT, and the impact of thyroid hormonal abnormalities and TAI on both the mother and unborn child.

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

The article by Othman *et al.* presented long term follow-up (mean 42 months) on 43 women who had presented with PPT and 146 controls who did not develop PPT. Ten of the 43 cases of PPT (23%) had developed permanent primary autoimmune hypothyroidism at the time of follow-up, compared with none of the controls.

Premawardhana LD, Parkes AB, Ammari F, John R, Darke C, Adams H, Lazarus JH 2000 Postpartum thyroiditis and long-term thyroid status: prognostic influence of thyroid peroxidase antibodies and ultrasound echogenicity. J Clin Endocrinol Metab 85:71–75

Stagnaro-Green A 2002 Clinical review 152: postpartum thyroiditis. J Clin Endocrinol Metab 87:4042–4027

Stagnaro-Green performed a comprehensive literature review and performed an analysis of incidence, presentation, and symptoms associated with PPT. A treatment algorithm was devised and a focused screening strategy was presented.

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

The article by Tachi *et al.* presented long-term follow-up (mean 8.7 yr) on 44 women who had presented with 59 episodes of PPT. Ten of the 44 women (29%) had developed permanent primary autoimmune hypothyroidism at the time of follow-up.

SECTION 8. SCREENING FOR THYROID DYSFUNCTION DURING PREGNANCY

8.2. BACKGROUND

The multitude of negative outcomes linked to thyroid abnormalities during pregnancy and postpartum has resulted in increased attention focused on screening for thyroid dysfunction in the peripartum period. Specifically, PPT, the possible association of thyroid hormonal abnormalities and miscarriage, thyroid antibodies and pregnancy loss in an unselected population, the possible association of recurrent abortion and thyroid antibody positivity, and subtle degrees of thyroid dysfunction and decreased IQ in the offspring, all contribute to the apparent merit of screening. However, a screening program is predicated on positive responses to the following questions:

1) Is the frequency of thyroid disease during pregnancy/postpartum sufficient to merit screening?

2) Are the sequelae of thyroid disease during pregnancy/postpartum significant?

3) Is a screening test available that is reliable, inexpensive, easily accessible, and accurate?

4) Have intervention strategies been shown to be safe and effective in decreasing the negative sequelae of thyroid disease during pregnancy/postpartum?

8.3. EVIDENCE

As detailed in prior sections of this report, the frequency of thyroid disease during pregnancy/postpartum is sufficient to warrant screening by measurement of TSH (and possibly by measurement of antithyroid antibodies), and adverse impact on both the mother and fetus is documented. Although the optimal algorithm for screening in the peripartum period has not been elucidated, cost-benefit analyses can be conducted to clarify this issue. A program to screen all 4.1 million pregnant women in the United States annually should be launched only if treatment strategies prove safe, efficacious, and cost-effective. To date only one randomized prospective intervention trial has been published (21). In that study, Negro *et al.* documented a significant decrease in the rate of spontaneous miscarriage and preterm delivery in euthyroid antibody-positive women treated with levothyroxine. However, although compelling, universal screening cannot be recommended on the basis of a single trial. A large scale randomized trial, the Controlled Antenatal Thyroid Study (CATS), is presently underway (280), the results of which will be of great importance in developing screening guidelines. Individual members of this committee believe that evidence is sufficient to justify screening all women before or during pregnancy, and this is common practice in some areas.

In addition to our own consideration, this committee requested the assistance of Dr. Victor Montori and his associates to review the available literature on screening. Over 500 abstracts were screened by the Montori group, and 56 papers were found to be eligible for further evaluation. Twenty-one of the papers were excluded on the basis of lacking an intervention component to the study. The remaining 35 papers were also excluded as they did not meet the criteria previously proposed. Consequently, the Montori group found, effectively, no studies that satisfied their criteria for forming the basis of a recommendation for/against screening. (The 35 studies that were reviewed in detail by the Montori group are listed below.)

The lack of evidence documenting treatment efficacy leaves the clinician in a quandary. Universal screening may be premature, but the association of thyroid abnormalities and untoward outcomes during pregnancy/postpartum is impossible to ignore. Therefore, aggressive case finding in high-risk populations may provide an appropriate balance between inaction and screening the entire population. Targeted screening is recommended for women, as listed below, who have an increased incidence of thyroid disease and in whom treatment for thyroid disease, if found, would be warranted. Targeted screening should be considered in women with clinical outcomes that have been associated with hypothyroidism but in whom treatment has yet to be shown to be beneficial (see below). Vaidya *et al.* (281) recently reported a study of screening by means of TSH, T_4, free T_4, and TPO-Ab in 1560 consecutive pregnant women. An important result was that screening only women considered

"high risk" on the basis of a personal or family history of thyroid disease, or a history of other autoimmune disease, would have missed 30% of women with overt or SCH.

The following are suggested indications for targeted thyroid disease case finding in pregnancy, since the incidence of clinical hypothyroid disease is high and benefit of therapy is clear:

1. Women with a history of hyperthyroid or hypothyroid disease, postpartum thyroiditis, or thyroid lobectomy
2. Women with a family history of thyroid disease
3. Women with a goiter
4. Women with thyroid antibodies (when known)
5. Women with symptoms or clinical signs suggestive of thyroid underfunction
6. Women with type I diabetes
7. Women with other autoimmune disorders
8. Women with infertility should have screening with TSH as part of their infertility work-up
9. Women with prior therapeutic head or neck irradiation.
10. Women with a prior history of preterm delivery.

Note that this list does not include women who currently have thyroid disease because presumably their thyroid function will be followed.

In the following conditions screening may be considered since the incidence might be high enough but no known benefit of treatment has yet been determined:

1. Women in whom the last delivery was preterm
2.1. Women with recurrent pregnancy loss.

This committee carefully considered all available data, including the analysis by consultants. We agreed with the conclusion that it is not possible to recommend universal screening, but believe that screening of selected patient groups is justified, based on the significant risks to offspring, the probable benefit of treatment, and the probable low incidence of adverse outcomes from intervention.

Screening should consist of a TSH measurement performed before pregnancy when possible, or at the first prenatal visit. If the TSH level is abnormal using a gestational age-dependent standard (see *Section 1*), then appropriate additional thyroid tests should be done. Treatment is not warranted for subclinical hyperthyroidism.

It should be noted that the committee does recommend TSH screening as part of the workup of infertility. It should also be noted that women living in iodine-deficient areas have a high risk for thyroid disease. In those areas, rather than general screening for hypothyroidism, efforts should be made to supplement women's diet with iodine before and during pregnancy (see *Section 6*).

Finally, a large-scale double-blind prospective study, entitled the "Controlled Antenatal Thyroid Screening Study," has been initiated by Lazarus and associates (280). Serum samples are obtained before 16 wk gestation, with half of the sera analyzed immediately for free T_4 and TSH, and the other half frozen until delivery. Women with a free T_4 below the 2.5th percentile and/or TSH above the 97.5th percentile receive levothyroxine therapy. The main outcome measure will be the development of the unborn child as measured at 3 yr of age. Outcome data, when available, will be instrumental

in beginning to develop a rational response to the screening controversy.

8.4. RECOMMENDATIONS

Although the benefits of universal screening for hypothyroidism may not be justified by current evidence, as presented in *Sections 1–7*, we recommend case finding among the following groups of women at high risk for thyroid dysfunction:

1. Women with a history of hyperthyroid or hypothyroid disease, PPT, or thyroid lobectomy
2. Women with a family history of thyroid disease
3. Women with a goiter
4. Women with thyroid antibodies (when known).
5. Women with symptoms or clinical signs suggestive of thyroid underfunction or overfunction, including anemia, elevated cholesterol, and hyponatremia
6. Women with type I diabetes
7. Women with other autoimmune disorders
8. Women with infertility should have screening with TSH as part of their infertility work-up.
9. Women with prior therapeutic head or neck irradiation.
10. Women with a prior history of miscarriage or preterm delivery

The USPSTF recommendation level is B; evidence is fair (GRADE 1|⊕⊕○○).

8.5. REMARKS

None.

8.6. PUBLICATIONS REVIEWED BY MONTORI AND ASSOCIATES:

1. **Lejeune B, Grun JP, de Nayer P, Servais G, Glinoer D** 1993 Antithyroid antibodies underlying thyroid abnormalities and miscarriage or pregnancy induced hypertension. Br J Obstet Gynaecol 100:669–672

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4. **Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen R** 2004 Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 351:241–249

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