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2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum

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Abstract

Background: Thyroid disease in pregnancy is a common clinical problem. Since the guidelines for the management of these disorders by the American Thyroid Association (ATA) were first published in 2011, significant clinical and scientific advances have occurred in the field. The aim of these guidelines is to inform clinicians, patients, researchers, and health policy makers on published evidence relating to the diagnosis and management of thyroid disease in women during pregnancy, preconception and the postpartum period.

Methods: The specific clinical questions addressed in these guidelines were based on prior versions of the guidelines, stakeholder input, and input of task force members. Task force panel members were educated on knowledge synthesis methods, including electronic database searching, review and selection of relevant citations, and critical appraisal of selected studies. Published English-language articles were eligible for inclusion. The American College of Physicians Guideline Grading System was used for critical appraisal of evidence and grading strength of recommendations. The guideline task force had complete editorial independence from the ATA. Competing interests of guideline task force members were regularly updated, managed, and communicated to the ATA and task force members.

Results: The revised guidelines for the management of thyroid disease in pregnancy include recommendations regarding the interpretation of thyroid function tests in pregnancy, iodine nutrition, thyroid autoantibodies and pregnancy complications, thyroid considerations in infertile women, hypothyroidism in pregnancy, thyrotoxicosis in pregnancy, thyroid nodules and cancer in pregnant women, fetal and neonatal considerations, thyroid disease and lactation, screening for thyroid dysfunction in pregnancy, and directions for future research.

Conclusions: We have developed evidence-based recommendations to inform clinical decision-making in the management of thyroid disease in pregnant and postpartum women. While all care must be individualized, such recommendations provide, in our opinion, optimal care paradigms for patients with these disorders.

These guidelines are dedicated to the memory of Dr. Peter Laurberg, our friend and colleague, who died tragically during their preparation.

I. Introduction

Pregnancy has a profound impact on the thyroid gland and its function. During pregnancy, the thyroid gland increases in size by 10% in iodine replete countries, but by 20% to 40% in areas of iodine deficiency. Production of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3), increases by nearly 50%, in conjunction with a separate 50% increase in the daily iodine requirement. These physiological changes happen seamlessly in healthy women, but thyroid dysfunction can occur in many pregnant women due to pathologic processes. Furthermore, other thyroid illnesses such as nodular disease and thyroid cancer are occaisonally detected during pregnancy, and may require treatment. Together, the burden of thyroid disease affecting women, either before, during, or directly after pregnancy, is substantial.

For these reasons thyroid function is frequently assessed during the gestation period. However, accurate assessment of maternal (and fetal) thyroid function during pregnancy remains difficult, and interpretation of laboratory testing differs from the non-pregnant patient. Placental human chorionic gonadotropin (hCG) stimulates thyroid hormone secretion, often decreasing maternal thyrotropin (TSH) concentrations, especially in early pregnancy. But while such transiently suppressed maternal TSH concentrations are often observed and deemed safe, defining the upper reference limit for serum TSH in this population has remained controversial. Furthermore, up to 18% of all pregnant women are thyroid peroxidase (TPOAb) or thyroglobulin antibody (TgAb) positive. Increasingly, data suggest that TPOAb positivity adversely modulates the impact of maternal thyroid status (especially hypothyroidism) on the pregnancy and the developing fetus. Thyroid antibody positivity separately increases the risk of thyroid dysfunction following delivery and during the postpartum period.

Studies have recently questioned the optimal treatment of hyperthyroidism during pregnancy. Clinical management of patients with Graves' disease is challenged by the understanding that maternal antibodies as well as antithyroid medication may differentially affect maternal and fetal thyroid function. Reports have also detailed the potential teratogenic effects of the antithyroid medications,methimazole (MMI) and propylthiouracil (PTU). But while mild hyperthyroidism appears safe for the mother and fetus, moderate to severe hyperthyroidism can prove dangerous. Thus, when and how to treat affected mothers during pregnancy remains an important clinical question. Following delivery, mothers often choose to breastfeed. Separate questions surround the optimal approach to the treatment of hypo- and hyperthyroidism while lactating.

Given the prevalence and potential dangers detailed above, many have suggested universally evaluating thyroid function in all women either before or during pregnancy. Such a

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screening mandate, however, must take the cost, effectiveness, and practical nature of any such approach into account. To date, studies evaluating this question appear to demonstrate mixed conclusions. Several ongoing investigations will shed further light on this difficult question.

Given the complexity surrounding thyroid physiology and thyroid illness during pregnancy and the postpartum period, how and when to evaluate for thyroid dysfunction, and how and if to treat thyroid illness during this period, remains challenging.

In 2011, the American Thyroid Association (ATA) first published guidelines on the diagnosis and management of thyroid disease during pregnancy and postpartum (1). There has been a substantial amount of new literature in this area since that publication.

It is in this context that the American Thyroid Association (ATA) charged a task force to develop revised clinical guidelines on the diagnosis and treatment of thyroid disease during pregnancy and the postpartum period. The task force consisted of both national and international experts in the field of thyroid disease and pregnancy, and included representatives from the ATA, the European Thyroid Association, the American College of Obstetricians and Gynecologists, the Society for Maternal Fetal Medicine and the Iodine Global Network. In addition to evidence-based updates of traditional content areas, the task force also sought to expand the prior document to address topics such as thyroid disease during lactation, the treatment of thyroid illness in infertile women and those undergoing assisted reproductive techniques (ART), as well as the approach to thyroid disease in the newborn.

Literature review for each section included an analysis of all primary studies in the area published since 1990, and selective review of the primary literature published prior to 1990 that was seminal in the field. In the past 25 years, there have been a number of recommendations and guideline statements relating to aspects of thyroid disease and pregnancy. In deriving the present guidelines, the task force conducted a new and comprehensive analysis of the primary literature and reformulated all clinical recommendations. In doing so, this document represents the best effort to create a useful, practical, and accurate guideline designed to help the practicing clinician, while also stimulating future research and discovery into this important and complex arena.

II. Methods

ATA Thyroid Disease in Pregnancy guidelines were previously published in 2011 (1). Because of the rapid growth of the literature relating to this topic, plans for revising the guidelines within ~4-5 years of publication were made at the inception of the project. Task force chairs were appointed by the ATA President with approval of the Board. A task force of specialists with complementary expertise (adult and pediatric endocrinology, obstetrics, maternal-fetal medicine, endocrine surgery, iodine nutrition, and epidemiology) was appointed. In order to have broad specialty and geographic representation, as well as fresh perspectives, approximately one-third of the task force is to be replaced for each iteration of the guidelines, as per ATA policy. In accordance with current ATA policies, the American College of Physicians Grading System was adopted for use in these guidelines (**Tables 1 and 2)** (2)**.**

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Prior to initiating the reviews, all task force members were provided written and verbal group advice on conducting electronic literature searches, critical appraisal of articles, and rationale for formulating strength of recommendations. Standardized data collection forms were used by all reviewers. For each question, a primary reviewer performed a literature search, appraised relevant literature, and generated recommendations, accompanying text, and a relevant bibliography. This was then reviewed by both chairs, revised as needed, and presented for review by the entire panel. Feedback and suggestions for revisions from the Chairs and panel members were obtained via e-mail, regularly scheduled teleconferences, and face-to-face meetings. Once the manuscript was drafted, all suggestions for revisions were regularly reviewed by the entire panel in the form of a tracked changes draft manuscript and teleconferences. The draft document continued to be revised until no suggestions for further revisions were requested by any panel members. Thus, general consensus on acceptability of recommendations and manuscript text was achieved, with the fundamental understanding that not all recommendations may be feasible in all practice settings, and adaptation of the guideline recommendations to individual care may be needed.

Formal stakeholder input in development of these guidelines was sought from ATA membership via an online survey distributed in October 2014. We also reviewed any letters, editorials, or reviews of the 2011 iteration of these guidelines (1) that were collected by the current chairs of the task force. Pre-publication verbal feedback on some of the key guideline recommendations was received at a formal Satellite Symposium held in conjunction with the Endocrine Society meeting in Boston on March 31, 2016. The guidelines were then provided to the ATA membership for review and comments over a two week period. The guideline manuscript was next reviewed and approved by the ATA Board of Directors. Feedback and suggestions were formally discussed by the panel, and revisions were made to the manuscript prior to journal submission. The organization of management guideline recommendations is shown in **Table 3**.

The medical opinions expressed here are those of the authors, and the task force had complete editorial independence from the ATA in writing the guidelines. No funding was received by individual task force members from the ATA or industry, for work on these guidelines. Competing interests of all task force members were reviewed at inception of the group, yearly, and upon completion of the guidelines, and are included with this document.

These Guidelines were approved by the Board of the ATA.

III. Thyroid Function Testing and Pregnancy

QUESTION 1 -HOW DO THYROID FUNCTION TESTS CHANGE DURING PREGNANCY?

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Normal pregnancy is associated with an increase in renal iodine excretion, an increase in thyroxine binding proteins, an increase in thyroid hormone production, and thyroid stimulatory effects of hCG. All of these factors influence thyroid function tests in the pregnant patient. The healthy thyroid adapts to these alterations, through changes in thyroid hormone metabolism, iodine uptake, and the regulation of the hypothalamic-pituitary-thyroid axis (3,4). The thyroid function tests of healthy pregnant women, therefore, differ from those of healthy non-pregnant women. Furthermore, the reference ranges for the most widely applied tests, TSH and free thyroxine (FT4), may vary significantly in different populations.

Following conception, circulating thyroxine binding globulin (TBG) and total T4 (TT4) concentrations increase by week 7 of gestation, and reach a peak by approximately week 16 of gestation (5). These concentrations then remain high until delivery. In the first trimester, maternal hCG directly stimulates the TSH receptor, increasing thyroid hormone production and resulting in a subsequent reduction in serum TSH concentration (4,6). Therefore, during pregnancy, women have lower serum TSH concentrations than before pregnancy, and a TSH below the nonpregnant lower limit of 0.4 mU/L is observed in as many as 15% of healthy women during the first trimester of pregnancy (7,8). In Japan, a suppressed TSH less than 0.6 mU/L is similarly frequently observed during the first trimester of pregnancy (9). The fraction of women with a suppressed TSH falls to about 10% in the second trimester, and 5% in the third trimester (4).

Measurement of free T4 (FT4) concentration by automated immunoassays results in a significant and assay dependent reduction in the measured serum FT4 concentrations in the third trimester, even though direct measurement of free T4 by more precise methods does not show a similar degree of reduction (4, 6,7). FT4 automated immunoassays, which are employed in most clinical laboratories, are complicated in pregnant women by the increase in TBG and decrease in albumin concentrations (10,11). Other methods of direct measurement, such as measurement by equilibrium dialysis, ultrafiltration, or liquid chromatography/tandem mass spectrometry (LC/MS/MS), are less influenced by the pregnancy-associated changes in serum proteins, but are significantly more expensive and less widely available. Thus, the automated immunoassays used for serum FT4 analysis are still widely used, but the important considerations discussed above must be noted. The use of population based, trimester-specific reference ranges remains the best way to handle this issue.

QUESTION 2 - WHAT IS THE NORMAL REFERENCE RANGE FOR SERUM TSH CONCENTRATIONS IN EACH TRIMESTER OF PREGNANCY?

There is a downward shift of the TSH reference range during pregnancy, with a reduction in both the lower (decreased by about 0.1-0.2 mU/L) and the upper limit of maternal TSH (decreased by about 0.5-1.0 mU/L), relative to the typical non-pregnant TSH reference range. The largest decrease in serum TSH is observed during the first trimester, due to elevated levels of serum hCG directly stimulating the TSH receptor and thereby increasing thyroid hormone production (**Table 4**). Thereafter, serum TSH and its reference range gradually rise in the 2nd and 3rd trimesters, but nonetheless remain lower than in non-pregnant women (12,13). Since hCG concentrations are higher in multiple pregnancies than in singleton pregnancies, the downward shift in the TSH reference interval is greater in twin pregnancies (11). In a study of 63

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women with hCG concentrations >200,000 IU/L, TSH was suppressed (≤0.2 mU/L) in 67% of women, and in 100% of women if hCG concentrations were >400,000 IU/L (14). Serum TSH reference range determinations should take into account iodine intake, TPO positivity, and according to some studies, body mass index (BMI).

Although the downward shift in TSH reference ranges is seen in essentially all populations, the extent of this reduction varies significantly between different racial and ethnic groups. Initial studies of pregnant women in the United States (U.S.) and Europe first led to recommendations for a TSH upper reference limit of 2.5 mU/L in the first trimester, and 3.0 mU/L in the 2nd and 3rd trimesters (1,15). However, more recent studies in pregnant women in Asia, India, and the Netherlands, have demonstrated only a modest reduction in the upper reference limit (16,17,18,19,20). A study of 4800 pregnant women in China recently showed that the downward shift in the TSH reference range occurred at weeks 7-12—but the upper reference limit was only reduced from 5.31 to 4.34 mU/L (17). Separate data from a recent prospective intervention trial in the United States support this finding (21). Analysis of the TSH and free T4 "set-point" in pregnant women showed that reductions in free T4 were observed only when the serum TSH was greater than 4.8 mU/L. Similar studies of pregnant women in India and Korea show a modest reduction in the first-trimester upper TSH limit of 0.5-1.0 mU/L. In some cases, this was not statistically different from the non-pregnant state (18,20). Thus, the current evidence supports only a slight downward shift in the upper reference range of TSH occurring in the latter first trimester of pregnancy, typically not seen prior to week seven (17).

A reduction in the lower TSH reference range is observed during pregnancy in almost all studies. In a small percentage of women, TSH can be undetectable (<0.01 mU/L), and yet still represent a normal pregnancy. In addressing the clinical importance of a reduced serum TSH during pregnancy, it is important to note that subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes. Therefore, a maternal TSH concentration that is low but detectable is likely not clinically significant (22). TSH ranges have been shown to vary slightly depending on different methods of analysis, although this is not clinically significant (23). One approach to reducing this variability is to use the Multiple of Medians calculation to compare values between assays. This calculation divides an individual value by the population median (24). The resulting value is not influenced by the differences between assays (24).

There is significant geographic and ethnic diversity in TSH concentrations during pregnancy, as shown in **Table 4.** The task force recognizes the limited availability of trimester-specific reference ranges calculated for most ethnic and racial populations with adequate iodine intake who are free of thyroid autoantibodies. Nonetheless, to provide guidance to all patients and clinicians, the panel recommends use of the following trimester-specific ranges and cutoffs when local assessments are not available. In the first trimester, the lower reference range of TSH can be reduced by approximately 0.4 mU/L, while the upper reference range is reduced by approximately 0.5 mU/L. For the typical patient in early pregnancy, this corresponds to a TSH upper reference limit of 4.0 mU/L. This reference limit should generally be applied beginning with the late first trimester, weeks 7-12, with a gradual return towards the non-pregnant range in the 2nd and 3rd trimesters. For specific recommendations regarding the diagnosis and treatment of maternal hypothyroidism, see Section VII.

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- **Recommendation 1**
  When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a healthcare provider's practice. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status. (***Strong recommendation, Moderate quality evidence)***

QUESTION 3 - WHAT IS THE OPTIMAL METHOD TO ASSESS SERUM T4 CONCENTRATION DURING PREGNANCY?

Unbound thyroxine represents only about 0.03% of serum total T4 content. Importantly, only free thyroxine is available for tissue uptake, with the remainder of T4 bound to serum proteins, primarily TBG. Serum total T4 concentrations are measured in the nanomolar range, while FT4 concentrations are measured in the picomolar range. In part because of this, measuring FT4 in the presence of high concentrations of bound T4 has proved to be challenging. This is especially true in conditions where binding-protein levels are altered, such as pregnancy.

Equilibrium dialysis and ultrafiltration are used for physical separation of serum free T4 from bound T4 prior to analysis of the dialysate or ultrafiltrate. While they are theoretically not influenced by changes in binding proteins and heterophilic antibodies, assays based on classical equilibrium dialysis or ultrafiltration are laborious, time-consuming, expensive, and not widely available.

As noted above, FT4 measurement performed by indirect analog immunoassays is used by the majority of clinical laboratories, largely due to its ability to be quickly performed on automated platforms. Unfortunately, this approach is prone to inaccuracy in the setting of pregnancy because of disruption of the original equilibrium – a process dependent upon dilution, temperature, buffer composition, affinity, and the concentration of the T4 antibody reagent and the T4-binding capacity within the serum sample (25). High protein concentrations in serum samples tend to result in higher FT4 values, whereas low protein concentrations are likely to yield lower FT4 values. In order to decrease nonspecific binding and neutralize the effect of nonesterified fatty acids (NEFA) on serum FT4, albumin is added in some assays. Albumin itself, however, binds T4 and when added in sufficient amounts, may disrupt the equilibrium. Nevertheless, the currently used FT4 immunoassays perform reasonably well in many circumstances, and most often accurately report both low FT4 levels in the setting of thyroid hormone deficiency and high FT4 levels in the setting of thyroid hormone excess (26,27).

Sera of pregnant women are characterized by higher concentrations of TBG and NEFA and by lower concentrations of albumin relative to the sera of non-pregnant women. In part because of this, many current FT4 analog immunoassays fail dilutional assessment (25,28). Because FT4 reference intervals in pregnancy vary widely between methods, interpretation of FT4 values requires method-specific as well as trimester-specific ranges (10,11,27). Whereas it is customary for manufacturers to suggest that laboratories establish their own reference range for such a test, this is frequently impractical for freeT4 assessment because it is especially difficult to recruit subjects with specific conditions such as pregnancy from which to independently establish method- and trimester-specific reference ranges. Therefore, it is

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customary for laboratories to adopt the pregnancy ranges provided by the test manufacturers. Typically, the characteristics of these reference pregnant cohorts are not disclosed, and differences in iodine intake and ethnicity may compromise the ability to generalize the manufacturer ranges across different populations. This problem adds to the complexity of accurate measurement of serum FT4 in the pregnant individual.

Current uncertainty around FT4 estimates in pregnancy has led some to question the wisdom of relying on any FT4 immunoassays during pregnancy (29,30). In contrast, measurement of total T4 and the calculated FT4 index (FTI) do show the expected inverse relationship with serum TSH (29). This suggests that TT4 measurements may be superior to immunoassay measurement of FT4 measurements in pregnant women. However, reference values should take the 50% increase in TBG witnessed during pregnancy by calculating the FT4 index using a serum thyroid hormone uptake test (such as the thyroid hormone binding ratio) into account. Changes in total serum T4 concentration through pregnancy among euthyroid women have been previously reported (5). Changes are predictable, with an increase in total T4 concentration from weeks 7-16 of gestation, ultimately reaching ~50% above the prepregnancy level. This level is then sustained through pregnancy. Therefore, a clinically acceptable upper range determination can be calculated by shifting the nonpregnant limit 50% higher. However, this can only be used after week 16 of pregnancy. If a T4 measurement is required before that time (i.e. weeks 7-16 of pregnancy), a calculation can be made for the upper reference range based on increasing the non-pregnant upper reference limit by 5% per week, beginning with week 7. For example, at 11 weeks of gestation (4 weeks beyond week 7), the upper reference range for T4 is increased by 20% (four weeks x 5%/week) (5).

As described above, free thyroid hormones can also be measured in the dialysate or ultrafiltrate using online solid phase extraction - liquid chromatography/tandem mass spectrometry (LC/MS/MS). However, this approach is time consuming, costly, and often impractical. Using direct equilibrium dialysis and LC/MS/MS, the 95% FT4 reference intervals decrease gradually with advancing gestational age: from 1.08-1.82 ng/dL in week 14 to 0.86-1.53 ng/dL in week 20 (31). Serum FT4 by LC/MS/MS correlates very well with serum FT4 measured by classical equilibrium dialysis, but correlation with results from the FT4 immunoassay are less satisfactory (8). The use of isotope dilution-LC/MS/MS for measuring T4 in the dialysate from equilibrium dialysis of serum is helpful to obtain a gold-standard reference measurement procedure for serum FT4 (32). This assay technology, unfortunately, is currently not widely available due to high instrument and operating costs.

- **Recommendation 2**
  The accuracy of serum Free T4 measurement by the indirect analog immunoassays is influenced by pregnancy and also varies significantly by manufacturer. If measured in pregnant women, assay method-specific and trimester-specific pregnancy reference ranges should be applied. **(*Strong recommendation, Moderate quality evidence)***

- **Recommendation 3**
  In lieu of measuring freeT4, total T4 measurement (with a pregnancy-adjusted reference range), is a highly reliable means of estimating hormone concentration during the last part of

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pregnancy. Accurate estimation of the free T4 concentrations can also be done by calculating a free thyroxine index. ***(Strong recommendation, Moderate quality evidence)***

IV. Iodine Status and Nutrition

Because of increased thyroid hormone production, increased renal iodine excretion, and fetal iodine requirements, dietary iodine requirements are higher in pregnancy than they are for nonpregnant adults (33). Women with adequate iodine intake before and during pregnancy have adequate intrathyroidal iodine stores and have no difficulty adapting to the increased demand for thyroid hormone during gestation. In these women, total-body iodine levels remain stable throughout pregnancy (34). However, in areas of even mild to moderate iodine deficiency, total-body iodine stores, as reflected by urinary iodine values, decline gradually from the first to the third trimester of pregnancy (35). Iodine, required for infant nutrition, is secreted into breast milk. Therefore, lactating women also have increased dietary iodine requirements (36).

Spot urinary iodine values are used most frequently for determination of iodine status in populations. Because there is substantial diurnal and day-to-day variation in urinary iodine excretion, urinary iodine concentrations cannot be used to identify particular individuals with iodine deficiency (37,38). Therefore, iodine levels are a population rather than individual marker and, outside unusual settings, urinary iodide testing is not beneficial for individual use.

- **Recommendation 4**
  Median urinary iodine concentrations can be used to assess the iodine status of populations, but single spot or 24-hour urine iodine concentrations are not a valid marker for the iodine nutritional status of individual patients. ***(Strong recommendation, High quality evidence)***

QUESTION 4 - WHAT IS THE IMPACT OF SEVERE IODINE DEFICIENCY ON THE MOTHER, FETUS, AND CHILD?

Maternal dietary iodine deficiency results in impaired maternal and fetal thyroid hormone synthesis. Low thyroid hormone values stimulate increased pituitary TSH production, and the increased TSH stimulates thyroid growth, resulting in maternal and fetal goiter (39). In areas of severe iodine deficiency thyroid nodules can be present in as many as 30% of pregnant women (40). Severe iodine deficiency in pregnant women has been associated with increased rates of pregnancy loss, stillbirth, and increased perinatal and infant mortality (41).

Normal levels of thyroid hormone are essential for neuronal migration, myelination and other structural changes of the fetal brain. As thyroid hormones are needed throughout pregnancy, iodine deficiency affects both maternal and fetal thyroid hormone production and insufficient iodine intake can lead to detrimental effects. Specifically, maternal and fetal iodine deficiency in pregnancy have adverse effects on the cognitive function of offspring

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(42,43,44,45). Children whose mothers were severely iodine deficient during pregnancy may exhibit cretinism, characterized by profound intellectual impairment, deaf-mutism, and motor rigidity. Iodine deficiency is the leading cause of preventable intellectual deficits worldwide (42).

Universal salt iodization is the most cost-effective way of delivering iodine and improving maternal and infant heath (46).

QUESTION 5 - WHAT IS THE IMPACT OF MILD TO MODERATE IODINE DEFICIENCY ON THE MOTHER, FETUS, AND CHILD?

Groups of pregnant women whose median urinary iodine concentrations are 50–150 μg/L are defined as mildly to moderately iodine deficient. Women with mild to moderate iodine deficiency during pregnancy are at increased risk for the development of goiter (39) and thyroid disorders (47). Low maternal UIC in pregnancy has been associated with reduced placental weight and neonatal head circumference (48). However, in areas with adequate dietary iodine intake, variations in maternal urinary iodine concentrations have a limited influence on physical developmental outcomes (49). Mild to moderate maternal iodine deficiency has also been associated with attention deficit and hyperactivity disorders in children (50) as well as impaired cognitive outcomes (51,52,53). In an iodine-deficient area iodized salt intake before pregnancy did improve maternal thyroid function; no difference in child neurodevelopment was noted (54), but improvement has been noted in other studies (55).

QUESTION 6 - WHAT IS THE IODINE STATUS OF PREGNANT AND BREASTFEEDING WOMEN IN THE UNITED STATES?

Surveillance of urinary iodine values of the U.S. population has been carried out at intervals since 1971. Following a precipitous drop in urinary iodine values between 1971 and 1994, U.S. dietary iodine intake has stabilized (56,57,58,59,60, 61). The U.S. population overall remains iodine sufficient. However, U.S. women of reproductive age are the most likely group to have low urinary iodine values. According to the World Health Organization (WHO) guidelines, median urinary iodine values for pregnant women between 149 and 249 μg/L are consistent with optimal iodine intake (42). In the 2005-2010 National Health and Nutrition Examination Survey (NHANES) surveys, the median urinary iodine concentration for U.S. pregnant women was 129 μg/L, consistent with mild iodine deficiency (62). Current data regarding iodine sufficiency among lactating U.S. women are very limited. It is possible that a subset of pregnant and lactating U.S. women may have mildly to moderately inadequate dietary iodine intake resulting in insufficient amounts of iodine in the breast milk to meet infants' dietary requirements, but studies have been small and inconsistent (63,64,65).

QUESTION 7- WHAT IS THE IODINE STATUS OF PREGNANT AND BREASTFEEDING WOMEN WORLDWIDE?

Since 1990, the number of households worldwide using iodized salt has risen from less than 20% to more than 70% (66). Despite these advances, however, 30 countries remain iodine deficient, and iodine deficiency remains the leading cause of preventable intellectual deficits

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worldwide (44). Recent reports highlight the value of iodized salt in correcting iodine deficiency states in India (67,68), although remaining iodine deficiency was noted in one report (69). Only 6% had low urinary iodine concentrations in rural Bangladesh (70), whereas 80% of pregnant women had low urine iodine concentrations in Pakistan (71). In Shanghai, China, iodine deficiency was noted in a subset of pregnant women (72), whereas in Shenyang city slight iodine excess was noted, with a consequent increase in subclinical hypothyroidism (73). Iodine status in Korea is more than adequate (median UIC 427 µg/L) (74). Iodine status in Japan is also more than adequate (median UIC 328 µg/L) (9). On the African continent, iodine status in pregnancy was inadequate in Niger (75), and was also poor in Ethiopia (76). Iodine nutrition in Iran was sufficient (77). In Brazil, median UIC was 138 µg/L, possibly due to reduced concentration of iodine in salt (78). In Europe many countries, including Belgium, the Czech Republic, Denmark, France, Latvia, Norway Spain, and the United Kingdom, have recorded significant iodine deficiency in their pregnant populations (47,79,80,81,82,83,84,85).

QUESTION 8- DOES IODINE SUPPLEMENTATION IN PREGNANCY AND LACTATION IMPROVE OUTCOMES IN SEVERE IODINE DEFICIENCY?

In areas of severe iodine deficiency, iodine supplementation of mothers prior to conception or in early pregnancy results in children with improved cognitive performance relative to children of mothers given a placebo (86,87,88). The prevalence of cretinism and other severe neurological abnormalities is significantly reduced (89). Maternal iodine supplementation in severely iodine-deficient areas also decreases rates of stillbirth and neonatal and infant mortality (90,91). Oral administration of iodized oil can increase birth weight in addition to correcting iodine deficiency (92).

A recent randomized clinical trial demonstrated that in moderately-to-severely iodine deficient areas without universal salt iodization, lactating women who receive one dose of 400 mg oral iodized oil after delivery can provide adequate iodine to their infants through breast milk for at least 6 months. Direct infant iodine supplementation was less effective at improving infant iodine status (93).

QUESTION 9 - DOES IODINE SUPPLEMENTATION IN PREGNANCY AND LACTATION IMPROVE OUTCOMES IN MILDLY TO MODERATELY IODINE-DEFICIENT WOMEN?

Eight controlled trials of iodine supplementation in mildly to moderately iodine-deficient pregnant European women have been published (94,95,96,97,98,99,100,101), although doses and timing of iodine supplementation varied and only two trials examined effects on offspring development. Iodine supplementation of moderately deficient pregnant women appears to consistently decrease maternal and neonatal thyroid volumes and Tg levels. Effects on maternal thyroid function have been mixed, with significant maternal TSH decreases with supplementation described in four (88,90,91,95) of the eight published trials, and increases in maternal T4 or FT4 noted in just two (90,95). A reduction in cord TSH also indicates improvement in gestational iodine status (102).

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In two non-randomized studies, neurodevelopmental outcomes were improved in children from mildly to moderately iodine-deficient areas whose mothers received iodine supplementation early in pregnancy (87,95). Another study failed to show neuropsychological improvement in 16 month old children of mothers who received supplementation (103). The timing of supplementation is likely to be critical because the beneficial effects of iodine on offspring development appeared to be lost if supplementation is started after 10–20 weeks gestation. If iodine supplementation is started before pregnancy in iodine deficient women better maternal thyroid function can be observed but, depending on dose and the timing of initiation, supplementation may not fully correct iodine deficiency in an already iodine-deficient population (104). A meta-analysis concluded that iodine supplementation improves some maternal thyroid indices and may benefit aspects of cognitive function in school age children, even in marginally iodine deficient areas (105). Another review highlighted the lack of high-quality evidence in relation to these outcomes and suggested that RCTs may not be feasible where iodine supplementation is common (106).

Recently, there has been controversy regarding whether it is ethical to perform randomized clinical trials of iodine supplementation in pregnancy in regions which are mildly to moderately iodine deficient (107,108,109). Caution in accepting the necessity of supplementation has been expressed, especially in areas where iodized salt is already in use (110).

No trials to date have specifically examined the effects of iodine supplementation in lactation in mildly to moderately iodine deficient regions.

QUESTION 10 - WHAT IS THE RECOMMENDED DAILY IODINE INTAKE IN WOMEN PLANNING PREGNANCY, WOMEN WHO ARE PREGNANT, AND WOMEN WHO ARE BREASTFEEDING?

Iodine is an essential nutrient required for thyroid hormone production and is primarily derived from the diet and from vitamin/mineral preparations. The U.S. Institute of Medicine recommended dietary allowances to be used as goals for individual total daily iodine intake (dietary and supplement), are 150 μg/d for women planning a pregnancy, 220 μg/d for pregnant women, and 290 μg/d for women who are breastfeeding (111). The WHO recommends 250 μg/d for pregnant and lactating women (39). This level is supported by a study of more than 7000 pregnant Chinese women in whom it was found that subclinical hypothyroidism and hypothyroxinemia were least common at the urinary iodine range of 150-249 μg/L, but risk for both these abnormalities rose when the urinary iodine concentration was lower or higher than this range (73).

Dietary iodine sources vary regionally. Sources of iodine in the United States diet have been difficult to identify, in part because there are a wide variety of potential sources and food iodine content is not listed on packaging. Iodized salt remains the mainstay of iodine deficiency disorder elimination efforts worldwide. However, salt iodization has never been mandated in the United States and only approximately 50% of salt sold for household use in the United States is iodized (112). In the United States, dairy foods are another important source of dietary iodine, due to iodine in cattle feed and the use of iodophor disinfectants by the dairy industry (113,114,115). Commercially-baked breads have been another major source of iodine in the

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United States due to the use of iodate bread conditioners (115). However, the use of iodate bread conditioners has decreased over the past several decades. Other sources of iodine in the United States diet are seafood, eggs, meat, and poultry (116). Foods of marine origin generally have high concentrations of iodine because marine animals concentrate iodine from seawater (96,97,98), although the amount of iodine in different fish and shellfish species is quite variable.

In the United States, the dietary iodine intake of individuals cannot be reliably ascertained either by patient history or by any laboratory measure. Due to concerns that a subset of pregnant U.S. women may be mildly to moderately iodine deficient and an inability to identify individual women who may be at risk, the ATA has previously recommended 150 μg daily iodine supplementation for all North American women who are pregnant or breastfeeding (117). More recently the Endocrine Society, Teratology Society, and American Academy of Pediatrics have also advocated iodine supplementation for pregnant and lactating U.S.women (15,118,119). The goal is supplementation of, rather than replacement for, dietary iodine intake. Special attention may need to be paid to those with dietary restrictions (e.g. lactose intolerant, gluten intolerant, low-carbohydrate, or vegan) as those individuals may have additional needs for supplementation (120).

Unfortunately, recommendations regarding iodine supplementation in the United States have not been widely adopted. In the NHANES 2001–2006 dataset, only 20% of pregnant women and 15% of lactating women reported ingesting iodine-containing supplements (121). When assessed in 2009, of the 223 types of prenatal multivitamins available in the United States, only 51% contained any iodine (122). However, this may recently have changed; in 2015 the Council for Responsible Nutrition, the U.S. supplement industry trade group, recommended that their members include 150 μg iodine in all prenatal multivitamin preparations. Iodine in U.S. prenatal multivitamins is typically derived either from potassium iodide (KI) or from kelp. The iodine content in prenatal multivitamin brands containing kelp may be inconsistent due to variability in kelp iodine content (123).Women consuming levothyroxine regularly do not require supplemental iodine, as the substrate is no longer needed for hormone formation.

The taskforce recommendations for iodine supplementation in the setting of lactation and breastfeeding are provided in Section XI.

- **Recommendation 5**
  All pregnant women should ingest approximately 250 μg iodine daily. To achieve a total of 250 μg iodine ingestion daily, strategies may need to be varied based on country of origin. ***(Strong recommendation, High-quality evidence)***

- **Recommendation 6**
  In most regions, including the United States, women who are planning pregnancy or currently pregnant, should supplement their diet with a daily oral supplement that contains 150 μg of iodine in the form of potassium iodide. This is optimally started 3 months in advance of planned pregnancy. ***(Strong recommendation, Moderate-quality evidence)***

- **Recommendation 7**
  In low-resource countries and regions where neither salt iodization nor daily iodine supplements are feasible, a single annual dose of ~400 mg iodized oil for pregnant women

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and women of childbearing age can be used as a temporary measure to protect vulnerable populations. This should not be employed as a long-term strategy or in regions where other options are available***. (Weak Recommendation, Moderate-quality evidence).***

- **Recommendation 8**
  There is no need to initiate iodine supplementation in pregnant women who are being treated for hyperthyroidism or who are taking LT4. ***(Weak recommendation, Low quality evidence)***

QUESTION 11 - WHAT IS THE SAFE UPPER LIMIT FOR IODINE CONSUMPTION IN PREGNANT AND BREASTFEEDING WOMEN?

Most people are tolerant of chronic excess dietary iodine intake due to a homeostatic mechanism known as the Wolff–Chaikoff effect (124,125). In response to a large iodine load, there is a transient inhibition of thyroid hormone synthesis. Following several days of continued exposure to high iodine levels, escape from the acute Wolff–Chaikoff effect is mediated by a decrease in the active transport of iodine into the thyroid gland, and thyroid hormone production resumes at normal levels (126).

Some individuals do not appropriately escape from the acute Wolff–Chaikoff effect, making them susceptible to hypothyroidism in the setting of high iodine intake. The fetus may be particularly susceptible, since the ability to escape from the acute Wolff–Chaikoff effect does not fully mature until about week 36 of gestation (127,128).

Tolerable upper intake levels for iodine have been established to determine the highest level of daily nutrient intake that is likely to be tolerated biologically and to pose no risk of adverse health effects for almost all individuals in the general population. The upper intake levels are based on total intake of a nutrient from food, water, and supplements and apply to chronic daily use. The U.S. Institute of Medicine has defined the tolerable upper limit for daily iodine intake as 1100 μg/d in all adults, including pregnant women (96) and the WHO has stated that daily iodine intake >500 μg may be excessive in pregnancy. Recent population data support the WHO threshold (73). The exception may be communities that have historically and consistently consumed greater > 500 μg daily without experiencing adverse effects (e.g. Japan).

Medications may be a source of excessive iodine intake for some individuals. Amiodarone, an antiarrhythmic agent (129), contains 75 mg iodine per 200 mg tablet. Iodinated intravenous radiographic contrast agents contain up to 380 mg/ml. Some topical antiseptics contain iodine, although systemic absorption is generally not clinically significant in adults except in patients with severe burns (130). Iodine-containing anti-asthmatic medications and expectorants are occasionally used. In addition, some dietary supplements such as kelp and some iodine preparations may contain very large amounts of iodine (several thousand times higher than the daily upper limit) and should not be taken. Ingestion of iodine and kelp supplements containing in excess of 500 μg/day is not recommended in pregnancy or lactation (131).

There is concern that some populations may be exposed to excess iodine. This may result in a high prevalence of thyroid dysfunction (132,133), an increased rate of hyperthyrotrophinemia (134), and an increased rate of hyperthyroid newborns (135). In addition,

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iodine-induced hypothyroidism has been reported in infants exposed to excess iodine from radiocontrast agents (136). It should be recognized that even low-dose iodine supplementation may trigger thyroid autoimmunity in a small proportion of women (73). The exception may be communities that have historically and consistently consumed greater > 500 μg daily without experiencing adverse effects. In one study, approximately one-third of Japanese pregnant women demonstrated higher urinary iodine concentration beyond 500 μg/Cr, but there were no problems in pregnancy progress and fetal development (9).

- **Recommendation 9**
  Excessive doses of iodine exposure during pregnancy should be avoided, except in preparation for the surgical treatment of Graves' disease. Clinicians should carefully weigh the risks and benefits when ordering medications or diagnostic tests that will result in high iodine exposure. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 10**
  Sustained iodine intake from diet and dietary supplements exceeding 500 μg daily should be avoided during pregnancy due to concerns about the potential for fetal thyroid dysfunction. ***(Strong recommendation, Moderate quality evidence)***

V. Thyroid Auto-Antibodies & Pregnancy Complications

QUESTION 12 - WHAT IS THE PREVALENCE OF THYROID AUTO-ANTIBODIES IN PREGNANT WOMEN?

Anti-thyroperoxidase or anti-thyroglobulin thyroid autoantibodies are present in 2 to 17% of unselected pregnant women (47,137,138,139,140,141,142,143,144). The prevalence of antibodies varies with ethnicity. In U.S.populations, thyroid antibodies are most frequent in Caucasian and Asian women and least frequent in African-Americans (139,145). Dietary iodine intake may also be associated with anti-thyroid Ab positivity during pregnancy. Shi and colleagues recently demonstrated a U-shaped relationship between urinary iodine concentrations and antibody positivity among pregnant women (73).

A recent study from Belgium in women seeking fertility treatment showed that both TPOAb and TgAb were present in 8% of women, while 5% demonstrated isolated Tg antibodies, and 4% demonstrated isolated TPOAb concentrations (146). Those women with isolated TgAb positivity had a significantly higher serum TSH than women without thyroid autoimmunity. While the committee acknowledges that testing for thyroid autoimmunity using only TPOAb would likely miss a small proportion of women with isolated Tg antibodies, we note that the vast majority of studies investigating thyroid autoimmunity and clinical outcomes used only TPOAb measurements. For this reason, the committee recommends assessment of TPOAb when testing for the presence of thyroid autoimmunity.

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QUESTION 13 - WHAT IS THE NATURAL HISTORY OF ANTITHYROID ANTIBODIES IN PREGNANT WOMEN?

QUESTION 14 - HOW SHOULD EUTHYROID, THYROID ANTIBODY POSITIVE WOMEN BE MONITORED DURING PREGNANCY?

In women with thyroid autoimmunity, hypothyroidism may occur due to the stress of pregnancy as the ability of the thyroid to augment hormone production is compromised. In 1994, Glinoer et al. performed a prospective study of 87 euthyroid (TSH ≤4 mU/L), TPO and/or TgAb positive women (147). Twenty percent of women in the study developed a serum TSH > 4 mU/L during gestation despite normal pre-pregnancy TSH values. Anti-thyroid Ab titers were highest in the first trimester, although they decreased by about 60% over the course of gestation. Twelve years later, in a prospective study, Negro et al. demonstrated similar results (28). The authors found that in TPOAb positive euthyroid women, TSH levels increased as gestation progressed, from a mean of 1.7 mU/L (12th week) to 3.5 mU/L (term), with 19% of women having a supra-normal TSH value at delivery. Because the risk of TSH elevation is increased in this population, increased surveillance of euthyroid thyroid antibody positive women should occur.

TPO antibodies are able to cross the placenta. At the time of delivery, cord blood TPOAb levels strongly correlate with third-trimester maternal TPOAb concentrations (148). However, maternal passage of either TPOAb or TgAb is not associated with fetal thyroid dysfunction.

- **Recommendation 11**
  Euthyroid, but TPO or Tg antibody positive pregnant women should have measurement of serum TSH concentration performed at time of pregnancy confirmation, and every 4 weeks through mid-pregnancy. (***Strong recommendation, High quality evidence***)

QUESTION 15 - SHOULD EUTHYROID WOMEN WITH THYROID AUTOIMMUNITY BE TREATED WITH SELENIUM?

Some studies evaluating non-pregnant women have shown that selenium is capable of diminishing TPOAb concentrations (149,150,151,152). However, this has not been observed in all studies (153). Negro et al. (154) noted that euthyroid, TPOAb positive pregnant women randomized to treatment with 200 µg/day selenium not only had a significant decrease in the frequency of postpartum thyroid dysfunction ($p<0.01$), but also had lower TPOAb concentrations during pregnancy compared to those in the untreated group. Importantly, this trial did not measure urinary iodine, a potential confounder since iodine status may influence the thyroidal effects of selenium. However, in another recent randomized clinical trial (155) performed in mildly iodine deficient British pregnant women, treatment with 60 mcg selenium daily did not affect TPO concentrations nor TPOAb positivity. Thus, conflicting data regarding selenium supplementation make any generalized recommendation unreliable, especially to regions with different iodine and/or selenium intakes. In addition, patients treated with selenium could be at higher risk for developing type 2 diabetes mellitus (156). For these reasons, the risk-to-benefit

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comparison does not presently support routine selenium supplementation of TPOAb positive women during pregnancy.

- **Recommendation12**
  Selenium supplementation is not recommended for the treatment of TPOAb positive women during pregnancy. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 16 - IS THERE AN ASSOCIATION BETWEEN THYROID ANTIBODIES AND SPORADIC SPONTANEOUS PREGNANCY LOSS IN EUTHYROID WOMEN?

Spontaneous pregnancy loss (miscarriage), occurs in 17-31% of all gestations (157,158). A spontaneous pregnancy loss is usually defined as one occurring at less than 20 weeks of gestation. The individual risk varies according to clinical factors including maternal age, family history, environmental exposures, and medical comorbidities (159). Pregnancy losses are a significant emotional burden to patients and may also result in bleeding, infection, pain, and need for surgical intervention.

Endocrine disorders have been previously recognized as risk factors for spontaneous pregnancy loss. Patients with poorly controlled diabetes mellitus may have up to a 50 % risk of loss (160). Thyroid dysfunction has similarly been associated with increased pregnancy loss (161). Stagnaro-Green and colleagues first demonstrated an association between pregnancy loss and thyroid antibodies in a prospective observational study. Patients who were positive for thyroid antibodies (TPOAb and/or TgAb) demonstrated a two-fold increase in the risk for pregnancy loss (17 % vs. 8.4 %, p=0.01) (162). Since that time, numerous other studies have examined the association between maternal anti-thyroid antibody status and pregnancy loss risk, showing similar findings. In a recent meta-analysis of eight case-control studies, the pooled OR for pregnancy loss in women with thyroid autoimmunity vs. women without anti-thyroid antibodies was 2.55 (95% CI 1.42-4.57). Meta-analysis of 14 cohort studies showed a similar increased OR of 2.31 (95% CI 1.90-2.82) (163). However, antibody-positive women were noted to be slightly older and to have slightly higher serum TSH values. In support of these data, a separate meta-analysis similarly found an increase in loss rate among thyroid Ab positive women (OR 3.90 for cohort studies; 95% CI 2.48-6.12; OR 1.80 for case control studies; 95% CI 1.25-2.60) (164).

Although a clear association has been demonstrated between thyroid antibodies and spontaneous pregnancy loss, this does not prove causality and the underlying mechanisms for such an association remain unclear. Three research groups have demonstrated one possible mechanism through increased fetal resorption in active immunization murine models (165,166,167). Several other mechanistic hypotheses have been proposed, including antibody-mediated mild thyroid hypofunction, cross-reactivity of anti-thyroid antibodies with hCG receptors on the zona pellucida, the presence of concurrent non-organ specific autoimmunity, and increased levels of endometrial cytokines in women with thyroid autoimmunity (168).

QUESTION 17 - IS THERE AN ASSOCIATION BETWEEN THYROID ANTIBODIES AND RECURRENT SPONTANEOUS PREGNANCY LOSS IN EUTHYROID WOMEN?

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Recurrent pregnancy loss is defined as either two consecutive spontaneous losses, or three or more spontaneous losses and may occur in up to 1% of all women (169). Several causes have been reported, including parental chromosomal anomalies, immunologic derangements, uterine pathology, and endocrine dysfunction (170).

In a case-control study, Iravani and colleagues reported that patients with primary recurrent pregnancy losses (3 or more) had a higher incidence of TgAb and/or TPOAb positivity. (OR 2.24 95 % CL 1.5-3.3) (171). Kutteh et al. reported similar findings, with an increased rate of TgAb and/or TPOAb positivity in 700 women with recurrent pregnancy loss as compared to 200 healthy controls (22.5% vs. 14.5%, p=0.01) (172). On the other hand, in a prospective observational study, Esplin and colleagues demonstrated no difference in TgAb and/or TPOAb positivity between patients with recurrent pregnancy loss and healthy controls (173). Pratt and colleagues reported a higher rate of subsequent pregnancy loss in patients with recurrent losses and thyroid antibody positivity (174). In a larger study with a similar population, Rushworth and colleagues reported no significant difference in live birth rates between women with recurrent losses who were TGAb or thyroid microsomal Ab positive and those who were not (175). In a case-control study, Lata et al. found that the prevalence of TPO antibodies was higher in women with recurrent pregnancy loss than in healthy pregnant controls without a history of recurrent loss (31% vs. 18%. P=0.031) (176). A meta-analysis of eight studies which included 460 antibody-positive patients and 1923 controls noted a significant association between thyroid antibody positivity and recurrent pregnancy loss (OR 2.3; 95% CI 1.5-3.5) (177).

Thus, the data for an association between thyroid antibodies and recurrent pregnancy loss are less robust than for sporadic loss. This may be because recurrent pregnancy loss has many potential causes, and endocrine dysfunction may only account for 15-20 % of all such cases (170). Many of the studies described above did not control for other potential causes of recurrent losses. One intriguing study reported an apparent interaction of anti-phospholipid antibodies (APAS) and anti-thyroid antibodies in the risk for recurrent pregnancy loss (178). In support of this, Kim and colleagues reported that women with recurrent pregnancy loss who were anti-thyroid antibody positive also demonstrated higher levels of anticardiolipin Ab and other non-organ-specific antibodies (179).

QUESTION 18 - DOES TREATMENT WITH LT4 OR IVIG DECREASE THE RISK FOR PREGNANCY LOSS IN EUTHYROID WOMEN WITH THYROID AUTOIMMUNITY?

Negro and colleagues reported a prospective, randomized interventional trial of levothyroxine in euthyroid patients who were TPOAb positive (28). They reported a significantly decreased rate of pregnancy loss in the levothyroxine-treated group (3.5 % vs. 13.8%, p<0.05). A limitation of the study is that the mean estimated gestational age at starting levothyroxine was ten weeks, and all but one of the eight losses in the untreated group had occurred before 11 weeks. This finding raises uncertainty as to the impact of the intervention upon the endpoint.

However, in a separate non-randomized, retrospective study, Lepoutre et al. analyzed data from 65 TPOAb positive pregnant women with serum TSH values of 1-3.5 mU/L at the first

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antenatal visit (180). Thirty-four of these women were treated with 50 µg LT4 daily starting at a mean 10 weeks gestation, while the others were not treated. None of the levothyroxine treated women miscarried, but 5 of 31 untreated women (16%) experienced pregnancy loss. Although limited in nature, these data support the findings of Negro et al. and begin to suggest a potential benefit to this treatment approach. The underlying mechanism is, however, uncertain.

Three small non-randomized case series have been published on the use of intravenous immunoglobulin therapy (IVIG) for the prevention of recurrent pregnancy loss in women with anti-thyroid antibodies (181,182,183). The live birth rates ranged from 80-95%, and the one study with a control group (consisting of women who refused IVIG therapy) reported a highly significant improvement in live births in the IVIG-treated cohort (95 % vs. 0% p=0.001) (182). Comparison of a levothyroxine intervention to an IVIG intervention in one study demonstrated a higher rate of term delivery in the levothyroxine treated group (183). However, all three studies have serious design flaws including small sample sizes, heterogeneous patient populations, lack of or limited randomization, and differences in the timing of treatment initiation. Nonetheless, intervention trials with levothyroxine (and less so IVIG) in TPOAb positive, euthyroid women with recurrent abortion appear to show a possible decrease in miscarriage rates. Further randomized trials are needed to better understand the effectiveness of both LT4 and IVIG intervention. At present, however, the cost, complexity and side effect profile associated with IVIG infusion must be noted, and make its use undesirable when compared to questionable benefit. In contrast, levothyroxine administration in low dosage (25-50 mcg/daily) is safe. Because of this, its use among patients with recurrent pregnancy loss may be reasonably considered, in the setting of early gestation, especially when no other known cause of prior pregnancy loss has been identified.

The task force makes note that two randomized clinical trials are currently ongoing. The Thyroid AntiBodies and LEvoThyroxine study (TABLET) trial in the United Kingdom is randomizing euthyroid, TPO antibody positive women with a history of infertility or recurrent losses to either levothyroxine vs. placebo, to assess effects on live birth rates. Separately, the T4Lifetrial in the Netherlands is examining the effects of levothyroxine treatment in euthyroid pregnant women with a history of recurrent loss. The primary outcome of this trial is the live birth rate.

- **Recommendation 13**
  Intravenous immunoglobulin treatment of euthyroid women with a history of recurrent pregnancy loss is not recommended. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 14**
  There is insufficient evidence to conclusively determine whether levothyroxine therapy decreases pregnancy loss risk in TPOAb positive, euthyroid women who are newly pregnant. However, administration of levothyroxine to TPOAb positive, euthyroid pregnant women with a prior history of loss may be considered given its potential benefits in comparison to its minimal risk. In such cases, 25-50 mcg of levothyroxine is a typical starting dose. ***(Weak recommendation, Low quality evidence)***

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QUESTION 19 - IS THERE AN ASSOCIATION BETWEEN THYROID AUTO-ANTIBODY POSITIVITY AND PREMATURE DELIVERY?

Preterm deliveries are defined as those occurring before 37 weeks gestation. In the US, 11.4% of all births are preterm (184). Preterm birth remains one of the most prevalent and morbid perinatal complications. It is the leading cause of neonatal death and is associated with increased risks for acute respiratory, gastrointestinal, immunologic, central nervous system, hearing, and vision problems, as well as longer-term motor, cognitive, visual, hearing, behavioral, and growth impairment (185). A decade ago, the annual cost of preterm delivery to the U.S.health care system was estimated at $26 billion (185). Preterm birth has remained difficult to predict, prevent, and treat primarily because there are multiple potential causes and pathways that end in premature labor (186). Examples include infection, trauma, cervical insufficiency, premature rupture of membranes, and maternal medical conditions.

The relationship between thyroid auto-antibodies and preterm delivery has been investigated with mixed results. Glinoer et al. reported in a prospective cohort that euthyroid women positive for either TPOAb or TGAb had a significantly increased incidence of preterm birth (16 % vs 8 %, p<0.005) (187). Ghafoor et al. evaluated 1500 euthyroid women and found an increase in preterm delivery in TPOAb positive women compared to women who were TPOAb negative (26.8% vs. 8.0%, p<0.01)(188). In contrast, Iijima et al. did not find an increased risk for preterm birth in women positive for seven different auto- and thyroid antibodies (189). This study had an unusually low rate of preterm birth in both study and control groups (3% vs. 3.1 %). Haddow et al. reported a significant increase in preterm premature rupture of the membranes, but not in preterm delivery, among women who were TPOAb and/or TGAb positive in the first trimester (190).

Importantly, three recent large prospective cohort studies failed to find significant associations between anti-thyroid antibody positivity and risk for premature delivery. However, in each of the studies, prematurity rates were nonsignificantly higher in TPOAb positive women than in women who were antibody negative (19,190,191). By contrast, Karakosta et al. found that euthyroid women (TSH <2.5 mIUl) with TPOAb and/or TGAb positivity in early pregnancy were at increased risk for spontaneous preterm delivery (RR 1.7, 95% CI 1.1-2.8) (192). In a small cohort of 395 pregnant women, Kumru and colleagues noted that spontaneous preterm delivery (< 37 weeks) was more frequent in TPOAb positive, euthyroid (TSH <2.6 mU/L) women (OR 2.5 ; 95% CI 1.06-5.89) (193). Negro and colleagues found that untreated TPOAb positive women had a substantially higher risk for preterm delivery than women without TPOAb (RR 12.18, 95% CI 7.93-18.7) (28). A 2011 meta-analysis of seven studies, including about 23,000 participants, concluded that there was an association between thyroid autoimmunity and preterm delivery (OR =1.6; 95% CI: 1.44-1.94) (194). In support, a meta-analysis of five cohort studies including 12,566 women similarly concluded that there was a positive association between the presence of thyroid Ab and preterm birth (OR 2.907, 95% CI 1.17-3.68) (164). Finally, a third meta-analysis of 11 prospective cohorts including 35,467 participants determined that the relative risk for delivery at less than 37 weeks for women with positive TgAb and/or TPOAb was 1.41 (95% CI 1.08-1.84) (195). Interestingly, in subgroup analyses, TPOAb, but not

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TGAb, positivity was associated with prematurity. Together, these data suggest that thyroid auto-antibody positivity is associated with increased risk for preterm delivery.

QUESTION 20 - DOES TREATMENT OF EUTHYROID, THYROID AUTO-ANTIBODY POSITIVE WOMEN WITH LEVOTHYROXINE REDUCE RISK FOR PREMATURE DELIVERY?

In contrast to association studies, interventional studies of levothyroxine therapy for the prevention of pre-term delivery are sparse. Negro reported an increased risk of preterm delivery among euthyroid TPOAb positive women compared to euthyroid TPOAb negative women in the only prospective interventional trial to date (22.4 % vs. 8.2 %, $p<0.01$) (28). The TPOAb positive subjects were randomized to either treatment with levothyroxine or no treatment, with the levothyroxine dose based on TSH level. The treated group had a significantly lower rate of preterm delivery than did the untreated group (7% vs. 22.4%, $p<0.05$). This finding has not been replicated. The ongoing TABLET study in the UK, a randomized clinical trial examining effects of LT4 treatment of euthyroid women with a history of infertility or recurrent pregnancy loss, will examine preterm birth as a secondary outcome. Therefore, at present, there are insufficient data from which to draw any conclusion regarding the utility of levothyroxine administration for the purpose of reducing preterm delivery.

- **Recommendation15**
  There is insufficient evidence to recommend for or against treating euthyroid, thyroid auto-antibody positive pregnant women with levothyroxine to prevent preterm delivery. ***(No recommendation, Insufficient evidence)***

QUESTION 21 - IS THYROID AUTOIMMUNITY IN EUTHYROID PREGNANT WOMEN ASSOCIATED WITH ADVERSE OBSTETRIC OR CHILD OUTCOMES OTHER THAN PREGNANCY LOSS AND PREMATURE BIRTH?

Antithyroid antibodies have been associated with perinatal death in some (191), but not all (140,196), studies. In two pregnancy cohorts an increased risk for placental abruption was observed in women with thyroid autoimmunity and without clinical hypothyroidism (140,190). Maternal thyroid autoimmunity has also been linked to postpartum depression (197,198) and to neonatal respiratory distress syndrome (196).

Several studies have examined associations between maternal thyroid autoimmunity and child development. In a nested case-control study, Li et al. reported lower motor and intellectual development at age 25-30 months in the offspring of euthyroid women who were TPOAb positive compared to children of TPOAb negative controls (199). Williams et al. followed 97 full-term mothers and their children, assessing child neurocognition at age 5.5 years (200). Lower perceptual performance and motor scores were described in children of TGAb positive mothers, and lower perceptual performance scores noted in children with TGAb positive cord blood. However, no neurodevelopmental outcomes were associated with maternal or infant TPOAb status. Wasserman and colleagues described higher rates of sensorineural hearing loss

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(22.7% vs. 4.3%, p=0.004) at age 8 in children whose mothers were TPOAb positive in pregnancy compared to children of TPOAb negative women. Although maternal thyroid function was not assessed in this study, the association remained significant after controlling for a known history of maternal hypothyroidism (141). In the same cohort, cognitive assessments were performed in children at ages 4 and 7 years (201). Maternal TPO antibody positivity was associated with lower child IQ at age 4, but effects were attenuated by age 7. The authors speculated that the lower IQ scores at age 4 might be mediated by sensorineural hearing loss. Ghassabian and colleagues assessed a cohort of 3139 mother/child pairs in which child cognitive function was assessed at age 2.5 years, and behavior assessed at age 3 (202). Maternal TPO antibody status did not predict child neurocognition, but TPOAb positivity was associated with externalizing problems in children (OR 1.64, 95% CI 1.17-2.29), especially attention deficit/hyperactivity problems (OR 1.77, 95% CI 1.15-2.72). This remained significant after adjustment for maternal TSH. Finally, Brown et al., in a nested case-control study, found that women with children on the autism spectrum were more likely to have had positive TPOAb during pregnancy than mothers of controls (203).

VI. The Impact of Thyroid illness upon Infertility and Assisted Reproduction

Infertility is defined as the failure to achieve a clinical pregnancy after 12 or more months of regular unprotected sexual intercourse (204). Infertility affects 7.4% of U.S.women aged 15-44 years (205). Infertility is due to female factors in about 35% of cases, due to male factors in 30% of cases, and due to both female and male factors in 20% of cases. In approximately 15% of cases the cause of infertility is unknown (206).

QUESTION 22- IS OVERT THYROID DYSFUNCTION ASSOCIATED WITH INFERTILITY IN WOMEN?

Irregular menses may occur in women with overt hyperthyroidism. Krassas and colleagues reported that menstrual irregularities were present in 22% of hyperthyroid patients as compared to 8% in age- and weight–matched euthyroid controls (207). However, in a cross-sectional study, the prevalence of hyperthyroidism (both subclinical and overt) was similar in infertile women compared to fertile controls (208).

The risk of infertility in women with overt hypothyroidism is less well studied. In a study of 171 hypothyroid women with TSH concentrations >15 mU/L, 68% reported having irregular menses, far higher than the 12% rate of menstrual irregularities reported by euthyroid controls (209). In one cross-sectional study among 129 infertile women, 5% had serum TSH levels >4.5 mU/L (210). In a separate cross-sectional study among women age 18-50 years, the prevalence of infertility was 52.3% in women with Graves' disease and 47% among women with

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Hashimoto's thyroiditis; however, thyroid function was not reported in either group (211). Thus, despite imperfect data, the majority of evidence appears to support an association between overt thyroid dysfunction and an increased risk of infertility. Thyroid dysfunction is also reversible, and treatment is generally safe and may exert a positive effect on fertility. Therefore, it is reasonable to treat overt thyroid dysfunction in infertile women, with the goal of normalizing thyroid function.

QUESTION 23 - IS SUBCLINICAL HYPOTHYROIDISM ASSOCIATED WITH INFERTILITY IN WOMEN?

Different definitions of subclinical hypothyroidism have been used in different studies examining this question, and results have been inconsistent. In a cross-sectional study of 704 women with infertility, the prevalence of TSH elevations was 2.3%, similar to background rates in the general population (212). In a prospective study, Poppe and colleagues did not find increased rates of subclinical hypothyroidism among infertile women, but did report slightly higher median serum TSH levels (1.3 vs. 1.1 mU/L) in the infertile women compared to controls (208). However, in a retrospective study, higher rates of subclinical hypothyroidism (13.9% vs. 3.9%) were reported in infertile women as compared to fertile controls (213). Among women with baseline TSH values 2.5-5 mU/L, TRH stimulation testing caused TSH increases to >30 mU/L in 46% of women with female-factor infertility vs. 7% of women whose infertility was due to male factors (214). Among women presenting with infertility, TSH levels were highest among women with ovulatory dysfunction and unknown causes of infertility, and lower among those women with tubal infertility and whose infertility was due to male factors (215). In an uncontrolled study, 94 infertile women with hypothyroidism (TSH >4.2 mU/L) were treated with LT4 (25-150 mcg/day) and 72 of them spontaneously conceived within one year (216). In a retrospective study, Yoshioka et al. reported that 84.1% of infertile female women with subclinical hypothyroidism (TSH>3.0 mU/L) successfully conceived and their infertility duration was shortened after LT4 therapy, suggesting that LT4 therapy may enhance fertility in patients with subclinical hypothyroidism (217). Importantly, whether or not LT4 treatment increases the likelihood of conception in subclinically hypothyroid women not undergoing ART has not been studied in controlled trials. Thus, there exist insufficient data to recommend for or against routine levothyroxine therapy in subclinically hypothyroid, thyroid auto-antibody negative infertile women who are attempting conception but are not undergoing ART.

QUESTION 24 - IS THYROID AUTOIMMUNITY LINKED TO INFERTILITY IN WOMEN?

Limited evidence suggests that women with female-factor infertility are more likely to have positive TPOAb than age-matched women who are not infertile, even if euthyroid (208). In addition, the prevalence of anti-thyroid antibodies may be higher in women with polycystic ovarian syndrome (PCOS) than in age-matched controls (218). Antithyroid antibodies are detectable in the ovarian follicles of women with thyroid autoimmunity, and correlate with serum antibody levels (219), although whether such antibodies interfere with the fertilization potential of maturing oocytes is unknown. Among infertile women with PCOS, the presence of antithyroid antibodies has been associated with a decreased likelihood of developing ovarian follicles in response to treatment with clomiphene citrate (220).

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- **Recommendation16**
  Evaluation of serum TSH concentration is recommended for all women seeking care for infertility. (***Weak recommendation, Moderate quality evidence)***

- **Recommendation 17**
  Levothyroxine treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy. (***Strong recommendation, Moderate quality evidence)***

- **Recommendation 18**
  There is insufficient evidence to determine if levothyroxine therapy improves fertility in subclinically hypothyroid, thyroid auto-antibody negative women who are attempting natural conception (not undergoing ART). However, administration of levothyroxine may be considered in this setting given its ability to prevent progression to more significant hypothyroidism once pregnancy is achieved. Furthermore, low dose levothyroxine therapy (25-50 mcg daily) carries minimal risk. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 19**
  There is insufficient evidence to determine if levothyroxine therapy improves fertility in nonpregnant, euthyroid, thyroid autoantibody positive women who are attempting natural conception (not undergoing ART). Therefore, no recommendation can be made for levothyroxine therapy in this setting. ***(No recommendation, Insufficient evidence***)

QUESTION 25 - IS MATERNAL SUBCLINICAL HYPOTHYROIDISM ASSOCIATED WITH WORSE ART OUTCOMES?

QUESTION 26 - DOES TREATMENT OF SUBCLINICALLY HYPOTHYROID WOMEN IMPROVE ART OUTCOMES?

In a retrospective cohort study among women undergoing intrauterine insemination (IUI), the use of LT4 to treat subclinical hypothyroidism (TSH >2.5 mU/L) was associated with higher pregnancy rates, and the use of LT4 to treat overt hypothyroidism with lower pregnancy rates, despite the fact that all LT4-treated patients had a serum TSH <2.5 at the time of IUI (221). In a separate prospective cohort study of 1477 women undergoing IUI, preconception serum TSH in the range of 0.4-4.99 mU/L was not associated with IUI parameters, pregnancy rates, or live birth rates per cycle (222).

The majority of evidence suggests that there is no difference in IVF outcomes between women with serum TSH <2.5 mU/L and those with very mild TSH elevations, defined as a TSH between 2.5-5 mU/L. A retrospective cohort of 195 IVF cycles which resulted in deliveries found that gestational age at birth was lower and mean birth weight was lower among women with preconception TSH >2.5 mU/L (223). In another retrospective cohort of 164 women undergoing IVF, clinical pregnancy rates were higher (22% vs. 9%, p=0.045) in women with TSH ≤2.5 vs. those with TSH >2.5 mU/L (224). However, in a retrospective cohort of 1055 women undergoing their first IVF cycle, in age-adjusted analyses there was no difference in pregnancy, pregnancy loss, or delivery rates among women with serum TSH <2.5 mU/L vs. those with TSH <4.5 mU/L (225). Another recent retrospective study examined IVF outcomes in

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627 women without known thyroid disease and concluded that the presence of pre-pregnancy subclinical hypothyroidism (serum TSH >4.5 mU/L) did not affect pregnancy rates, live birth rates, or miscarriage rates (226). A case-control study among women undergoing first IVF cycles found no difference in embryo quality among women with serum TSH 0.45-2.5 vs. 2.5-4.5 mU/L (227). Another retrospective cohort similarly reported no associations between serum TSH in the range of 0.5-4.5 mU/L and IVF outcomes (228). Finally, in a retrospective study which aimed to control for embryo quality by limiting the cohort to 1599 euploid blastocyst transfer cycles, variations in serum TSH ≤2.5 mU/L were not associated with differences in implantation, pregnancy loss, or live birth rates (229).

However, data generally demonstrate that treatment of more significant elevations in TSH concentrations (although still classified as subclinical hypothyroidism) appears beneficial. A randomized clinical trial was conducted in women aged 20-40 years with subclinical hypothyroidism (serum TSH >4.5 mU/L with normal free T4) who were undergoing IVF (230). A total of 64 women were randomized to treatment with LT4 (50 mcg daily starting at the time of initiation of ovarian stimulation, and titrated to maintain TSH <2.5 mU/L in the first trimester in those women who did achieve pregnancy) vs. placebo. The treated women had higher rates of clinical pregnancy, lower rates of miscarriage, and higher delivery rates. Another trial randomized 64 infertile women with subclinical hypothyroidism (TSH >4.2 mU/L with normal free T4) to treatment with 50 mcg/day LT4 vs. placebo and similarly reported higher pregnancy rates, lower pregnancy loss rates, and higher live birth rates in the treated women than in the control group (231). A recent meta-analysis pooled results of these trials with a third study (232) examining the effects of LT4 treatment for TPOAb positive euthyroid women undergoing ART and concluded that although LT4 treatment did not have any effect on clinical pregnancy rates (pooled relative risk 1.75, 95% CI 0.90-3.38), it did result in a higher delivery rate (pooled relative risk 2.76, 95% CI 1.20-6.44) (233).

Together, these data suggest that subclinical hypothyroidism likely impacts ART in a dose-related fashion, such that impact worsens as TSH concentrations rise. It is also well known that TSH concentrations are variable, and may differ by several mU/L from week to week, despite no change in treatment (234). It therefore seems prudent to recommend treatment of subclinically hypothyroid women seeking pregnancy with ART for any TSH elevation >2.5 mU/L.

- **Recommendation 20**
  Subclinically hypothyroid women undergoing IVF or ICSI should be treated with levothyroxine. The goal of treatment is to achieve a TSH concentration <2.5 mU/L. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 27- IS TREATED MATERNAL HYPOTHYROIDISM ASSOCIATED WITH WORSE ART OUTCOMES COMPARED TO HEALTHY CONTROLS?

In a retrospective cohort study, among 240 women aged ≤37 years undergoing first IVF retrieval cycles, 21 euthyroid (serum TSH 0.35-4.0 mU/L) women with treated hypothyroidism had lower pregnancy rates than the women without thyroid disease (235). However, a subsequent

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case-control study including 137 LT4-treated hypothyroid women (mean serum TSH 1.6±0.7 mU/L) and 274 age-matched euthyroid controls determined that the presence of adequately treated hypothyroidism was not associated with inferior rates of pregnancy, implantation, or live birth following IVF/ICSI (236). Thus, no conclusion can be drawn from these data.

QUESTION 28 - IS MATERNAL ANTITHYROID AB POSITIVITY ASSOCIATED WITH POORER OUTCOMES FOLLOWING ASSISTED REPRODUCTIVE TECHNOLOGY?

Studies examining ART outcomes in thyroid auto-antibody positive and negative women have enrolled heterogeneous populations with differing underlying etiologies for infertility. Some, but not all, studies have been limited to women who were euthyroid. Different ART/IVF protocols have also been employed, in different places and over time. A meta-analysis of prospective cohort studies suggests that pregnancy rates following IVF do not differ between antibody positive and negative women, but, as discussed previously (see Section V), that risk of pregnancy loss is higher in those women with positive thyroid auto-antibodies (237). However, a recent retrospective study examined IVF outcomes in 627 women without known thyroid disease and concluded that the presence of pre-pregnancy thyroid autoimmunity did not affect pregnancy rates, live birth rates, or pregnancy loss rates (226). Similarly, two recent retrospective cohorts reported no differences in pregnancy, pregnancy loss, or live birth rates in thyroid antibody positive vs. negative euthyroid women undergoing IVF with ICSI (238,239). Separately, a prospective cohort study found no differences in outcomes of IVF with ICSI in TPO and/or TGAb positive vs. negative euthyroid women (240). By contrast, a recent retrospective IVF cohort found that fertilization, implantation, and pregnancy rates were lower in 90 antithyroid antibody positive compared to 676 antibody negative women, but thyroid function was not reported in either group (241).

QUESTION 29 - DOES TREATMENT OF ANTI-THYROID AB POSITIVE, EUTHYROID WOMEN IMPROVE ART OUTCOMES?

Based on a single small randomized clinical trial and one retrospective cohort trial, levothyroxine treatment for thyroid antibody positive women without thyroid dysfunction undergoing IVF does not appear to improve outcomes (232,242). Two small trials suggest the potential for improved pregnancy rates in thyroid antibody positive infertile women who are treated with glucocorticoids prior to ART (243,244). In the trial by Litwicka et al., 60 euthyroid (TSH <2.5 mU/L) TPO and/or TGAb positive women undergoing IVF were randomized to prednisolone 5 mg daily starting from the day of oocyte retrieval and continuing through the first trimester. There were higher overall pregnancy (60% vs 30%, p=0.02) and live birth (46.6% vs. 20%, p=0.05) rates in the treated vs. untreated women (243). Turi and colleagues randomized 48 TPOAb positive infertile women to prednisone vs. placebo for four weeks before intrauterine insemination (244). The pregnancy rate was 33.3% in treated women compared to 8.4% in the placebo group (p=0.03). Pregnancy loss rates were not significantly different between the two groups. Although these small trials appear promising, the risks of corticosteroid use in early pregnancy are not well understood (245).

- **Recommendation 21**

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There is insufficient evidence to determine whether levothyroxine therapy improves the success of pregnancy following ART in TPOAb positive, euthyroid women. However, administration of levothyroxine to TPOAb positive, euthyroid women undergoing ART may be considered given its potential benefits in comparison to its minimal risk. In such cases, 25-50 mcg of levothyroxine is a typical starting dose. ***(Weak Recommendation, Low quality evidence)***

- **Recommendation 22**
  Glucocorticoid therapy is not recommended for euthyroid, thyroid auto-antibody positive women undergoing ART. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 30 - DOES OVARIAN HYPERSTIMULATION ALTER THYROID FUNCTION?

Although there are multiple ART protocols currently in use, protocols for IVF or IVF with ICSI typically begin by inducing controlled ovarian hyperstimulation through the use of gonadotrophins, gonadotrophin-releasing hormone analogues, or GnRH antagonists in combination with gonadotrophins. Follicular development is monitored by ultrasound, and when leading follicles are large enough, hCG is administered in order to produce fully mature oocytes. Controlled ovarian hyperstimulation causes serum estradiol to rapidly rise to supraphysiologic levels (4000-6000 ng/L), comparable to those detected in late pregnancy (246). These hormonal manipulations may alter thyroid function. The presumed mechanism for this effect relates to the rise in TBG associated with high estrogen levels, which reduce free thyroid hormone concentrations and, in turn, feed back to cause serum TSH elevations. In addition, the administered hCG can directly stimulate thyroidal TSH receptors, causing increases in thyroid hormone and subsequent decreases in TSH. A systematic review (247) found inconsistent effects of ovarian stimulation on serum thyroid hormones. For example, during and up to one month after ovarian stimulation serum TSH was increased in 3 of 5 studies, while free T4 was increased in 2 studies, decreased in one study, and unchanged in another. In some women (248, 249,250), serum TSH levels increased to ≥2.5 mU/L following ovarian stimulation. Gracia and colleagues reported increases in both serum TSH and free T4 during ovarian stimulation which peaked one week after hCG administration, with 44% of the women with baseline TSH ≤2.5 mU/L having increases to >2.5 mU/L (251). Reinblatt et al. reported that serum TSH increased in parallel with serum estradiol during the course of ovarian stimulation, with more marked TSH increases seen among TPO-positive women (252).

Ovarian hyperstimulation syndrome (OHSS) is a complication of controlled ovarian hyperstimulation in which increased vascular permeability results in fluid shifts from intravascular to third space compartments. Mild OHSS, manifested by mild ascites and abdominal symptoms, occurs in up to 20-33% of all IVF cycles. Severe OHSS, which occurs in 0.1-2% of IVF cycles, may be associated with thrombosis and respiratory distress, and is occasionally fatal (253). A recent case report described a patient who had subclinical hypothyroidism prior to IVF which was adequately treated with levothyroxine. The patient rapidly developed overt hypothyroidism in the setting of severe OHSS (254). However, Poppe et al. prospectively studied thyroid function in women undergoing controlled ovarian

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hyperstimulation and found no differences in serum TSH or FT4 levels between 25 women who developed OHSS and 52 women who did not (246).

Among women with adequately treated hypothyroidism (i.e. receiving LT4 therapy), ovarian stimulation has been reported to induce hypothyroidism by the time of egg retrieval (255). In one cohort study, increases in serum TSH during ovarian stimulation were more marked in LT4-treated women than in women without underlying hypothyroidism one week after hCG administration. However, TSH levels no longer differed between the groups by the time of pregnancy testing (251). In a prospective cohort study in 72 treated hypothyroid women with serum TSH <2.5 mU/L prior to ovarian stimulation, serum TSH rose sequentially from 1.7±0.7 mU/L at baseline to 2.9±1.3 mU/L at the time of hCG administration, and to 3.2±1.7 mU/L 16 days after hCG, with serum hCG >2.5 mU/L in 46 (64%) of subjects by the time hCG was administered (256). A retrospective cohort study demonstrated that among treated hypothyroid women who undergo IVF, 84% required LT4 dose increases, most within the first 5-7 weeks of gestation (257). However, a small prospective study found that treated hypothyroid patients who conceived with the help of gonadotrophin therapy did not require larger LT4 dose increases than treated hypothyroid women who conceived spontaneously (258).

- **Recommendation 23**
  When possible, thyroid function testing should be performed either before or 1-2 weeks after controlled ovarian hyperstimulation, since results obtained during the course of controlled ovarian stimulation may be difficult to interpret. ***(Weak recommendation, Moderate quality evidence)***

- **Recommendation 24**
  In women who achieve pregnancy following controlled ovarian hyperstimulation, TSH elevations should be treated according to the recommendations outlined in Section VII. In non-pregnant women with mild TSH elevations following controlled ovarian stimulation, serum TSH measurements should be repeated in 2-4 weeks, since levels may normalize. ***(Weak recommendation, Moderate quality evidence)***

VII. Hypothyroidism and Pregnancy

Primary overt maternal hypothyroidism is generally defined as the presence of an elevated TSH and a decreased serum FT4 concentration during gestation, with both concentrations outside the (trimester-specific) reference ranges. In very rare cases, it is important to exclude other causes of abnormal thyroid function such as TSH-secreting pituitary tumors, thyroid hormone resistance, or central hypothyroidism with biologically inactive TSH. Several investigations report that at least 2-3% of healthy, non-pregnant women of childbearing age have an elevated serum TSH (259,260). The prevalence may be higher in areas of iodine insufficiency. When iodine nutrition is adequate, the most frequent cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis). Therefore, not surprisingly, thyroid autoantibodies can be detected in ~30-60% of pregnant women with an elevated TSH concentration (19,260,261).

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In the 2011 ATA guidelines, the upper reference limit for serum TSH concentration during pregnancy was defined as 2.5 mU/l in the first trimester, and 3.0 mU/l in the second and third trimesters. These cutoffs were predominantly based on the published reference ranges obtained from six pregnancy studies together comprising a total cohort of approximately 5500 subjects (12,13,18,262, 263,264). Since that publication, additional much larger cohorts have published center- and trimester specific pregnancy reference ranges. These analyses combine data from over 60,000 subjects (17,24,265,266,267,268). Importantly, this larger analysis demonstrates substantial population differences in the TSH upper-reference limit (**Table 4**) (17,24,142,262,264,265,266,267,268,269,270,271,272,273,274). These differences may be partly attributable to differences in the iodine status between populations, as well as the TSH assays used for analysis. However, these data also demonstrate important influences of BMI, geography, and ethnicity upon 'normalcy'of TSH concentrations in pregnant women. In summary, substantial variation exists between populations, with many recent investigations confirming a more liberal upper TSH reference range in healthy pregnant women with no thyroid disease (269). Equally important, recent studies have also demonstrated an important additive influence of TPOAb positivity upon maternal thyroid status. Increasingly, there appears to be a greater risk for adverse events in women who are TPOAb positive in comparison to those who are TPOAb negative, even when thyroid function is identical. The reasons for this remain unclear. As described in Section V, some studies suggest that euthyroid, TPOAb positive women may be at increased risk for adverse clinical outcomes not observed in TPOAb negative comparators (19). As a consequence, it is difficult to precisely define a universal TSH cut-off above which LT4 therapy should be initiated for all pregnant women. Rather, decisions about levothyroxine treatment must be based upon both measurement of thyroid function and TPOAb status.

QUESTION 31 - WHAT IS THE DEFINITION OF HYPOTHYROIDISM IN PREGNANCY?

Elevations in serum TSH concentrations during pregnancy should ideally be defined using pregnancy- and population-specific reference ranges. It is important to note that detection of an increased TSH concentration is not always synonymous with decreased FT4 concentrations. Frequently, elevated maternal TSH is detected when FT4 concentrations are normal. Conversely, low FT4 concentrations can be detected despite normal TSH concentrations. The latter situation is referred to as isolated hypothyroxinemia. Excepting the very rare scenarios noted above, serum TSH measurement remains the principal determinant of maternal thyroid status at the present time, and should be used to guide treatment decisions and goals. Since there are substantial differences in the upper reference limit for TSH between different populations (**Table 4**), each practitioner and hospital should ideally seek to determine their own trimester specific reference ranges, obtained from analysis of healthy, TPOAb negative, and iodine sufficient women. However, the task force recognizes that this is frequently not feasible. Therefore, this guideline also provides a practical guide for clinicians, proposing a stepwise approach to evaluation.

- **Recommendation 25**

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In the setting of pregnancy, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range. (***Strong recommendation, High quality evidence)***

- **Recommendation 26**

The pregnancy-specific TSH reference range should be defined as follows:

- When available, population and trimester-specific reference ranges for serum TSH during pregnancy should be defined by a provider's institute / laboratory, and should represent the typical population for whom care is provided. Reference ranges should be defined in healthy, TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness. (***Strong recommendation, High quality evidence)***
- When this is not feasible, pregnancy-specific TSH reference ranges obtained from similar patient populations, and performed using similar TSH assays should be substituted. (**Table 4**). ***(Strong recommendation, High quality evidence)***
- If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ~ 4.0mU/l may be used. For most assays, this represents a reduction in the non-pregnant TSH upper reference limit of ~0.5 mU/L. ***(Strong recommendation, Moderate quality evidence***)

QUESTION 32 - HOW IS ISOLATED HYPOTHYROXINEMIA DEFINED IN PREGNANCY?

Isolated hypothyroxinemia is typically defined as a free thyroxine concentration in the lower 2.5th -5th percentile of a given population, in conjunction with a normal maternal TSH concentration.

QUESTION 33 - WHAT ADVERSE OUTCOMES ARE ASSOCIATED WITH OVERT HYPOTHYROIDISM DURING PREGNANCY?

Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications (275) as well as detrimental effects upon fetal neurocognitive development (276). Specific adverse outcomes associated with overt maternal hypothyroidism include increased risks of premature birth, low birth weight, pregnancy loss, and lower offspring intelligence quotient (IQ). Abalovich et al. demonstrated that women with overt hypothyroidism carry an estimated 60% risk of fetal loss when not adequately treated (277). Separately, Leung et al. demonstrated a 22% risk of gestational hypertension in pregnant women with overt maternal hypothyroidism (278). Finally, Allan et al. similarly described an increased risk of fetal death among pregnant women with overt disease (260). Together, these data demonstrate a clear association between overt maternal hypothyroidism and risk to the maternal-fetal unit.

QUESTION 34 - WHAT ADVERSE OUTCOMES ARE ASSOCIATED WITH SUBCLINICAL HYPOTHYROIDISM DURING PREGNANCY?

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Subclinical hypothyroidism is variably associated with an increased risk of adverse pregnancy outcomes in most, but not all studies. This is in part due to the fact that separate studies use differing cut-offs to define an elevated TSH concentration. Also, many studies do not account for TPOAb status. **Table 5** provides an overview of all available observational and prospective studies (inclusive of at least 400 subjects) investigating the effect of maternal subclinical hypothyroidism upon pregnancy (19,192,193,259,279,280,281,282,283,284,285,287,288,289,291,294,295,306,314,318). Separately, **Table 6** describes the additive adverse impact of TPOAb status upon maternal hypothyroidism (19,192,279,284,287,288,289,291,295,314).

For the purposes of discussion, the investigations that have studied the association between elevated maternal TSH concentration and adverse clinical endpoints can be broadly grouped into three categories below based upon adverse endpoints. These include adverse effects on pregnancy outcome (i.e. pregnancy loss), adverse perinatal outcomes (i.e. premature delivery, hypertensive disorders), and adverse neurocognitive outcomes (IQ) in offspring.

Pregnancy loss

Early fetal loss naturally occurs in approximately 30% of pregnancies. Since the majority of pregnancy losses occur even before pregnancy is clinically recognized, pregnancy loss is a difficult study endpoint (158). Nevertheless, different studies have suggested a relationship between higher levels of maternal TSH and pregnancy loss. Negro et al. (286) reported a significantly higher pregnancy loss rate in TPOAb negative women with TSH concentrations between 2.5-5.0 mU/L compared to those with TSH concentrations below 2.5 mU/L (6.1% vs. 3.6%). Similarly, Benhadi et al. performed a prospective cohort study investigating the risk of pregnancy loss (defined as miscarriage, or fetal or neonatal death) in 2497 Dutch women. In this cohort of pregnant women without overt hypothyroidism, the risk of child loss increased with higher levels of maternal TSH (287), although results should be interpreted with caution given the very small number of 27 cases studied, as well as the heterogeneity of the study's endpoint. In an Australian cohort, early-pregnancy TSH levels >95th percentile were associated with an increased risk of miscarriage (OR 3.66) although subclinical and overt hypothyroid cases were pooled (292). A separate retrospective study that determined thyroid parameters in early-pregnancy samples obtained from 202 pregnancies that subsequently miscarried showed higher mean TSH and lower FT4 concentrations, as well as a higher prevalence of TSH concentrations > 97.5th percentile and FT4 concentrations < 2.5th percentile compared to 3,592 normal pregnancies (137). More recently, Liu and colleagues demonstrated a graded increase in miscarriage risk as maternal TSH concentrations increased. This effect was augmented by the presence of TPOAb positivity (288).

Negro et al. published data suggesting that subclinical hypothyroidism increases the risk of pregnancy complications in TPOAb positive women (286). In this prospective trial of >4600 subjects, women were randomized to universal screening versus case finding (high-risk screening) during pregnancy, with subsequent levothyroxine treatment of anti-TPO positive women with TSH >2.5 mU/L. Low-risk women in the unscreened group had serum collected and stored for analysis postpartum. Within the subset of women classified as low-risk for hypothyroidism, treatment of TPOAb positive women with TSH >2.5 mU/l resulted in a

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significant reduction in a composite endpoint of pregnancy complications when compared with no treatment. The composite endpoint remains a significant study limitation, as many variables were subjective in nature. Furthermore, it is critical to note that the primary study endpoint was non-superior, showing no benefit of universal screening and treatment (286) when compared with screening of high-risk women only. This is because the primary, pre-defined endpoint analyzed the effects of LT4 treatment on both low-risk and high-risk subjects together. Importantly, all high-risk women in the study were tested and treated for elevated TSH values. Therefore, when combining both groups, the treatment effect on the low-risk group was diluted leading to the conclusion of no superiority of universal screening. As such, this study should be viewed as providing important and provocative data, worthy of further study (286). However, its conclusion that universal screening did not confer a benefit, combined with the difficulty in drawing conclusions from a composite endpoint, make it challenging to translate into clinical practice.

Premature delivery & Other Pregnancy Complications

The largest study investigating the association of maternal hypothyroidism and premature delivery was performed by Casey et al. in a cohort of 17,298 pregnant women presenting for prenatal care (261). Subclinical hypothyroidism was associated with an increased risk of premature delivery < 34 weeks (4% vs. 2.5%, p=0.01), but not with premature delivery <32 weeks (2.5 vs. 1%, p=0.07), or <36 weeks (7 vs. 6%, p=0.39). This lack of continuous effect raises questions about the 34-week finding. A later study by Cleary-Goldman et al. showed no association of an elevated TSH with prematurity <37 weeks (289). Separately, other studies have also investigated this potential adverse relationship, albeit with conflicting results (192,260,266286,290,291,292). This variation can, in part, be explained by the fact that some studies pooled overt and subclinical hypothyroid cases together (260, 292), while others used different TSH cut-off values (286,290), and yet others enrolled a very limited number of subjects (192,291). A recent study compared the value of using population-based reference range limits (TSH > 97.5 percentile, defined as 4.0 mU/L) versus a fixed TSH cutoff of 2.5 mU/L (19). While a TSH >2.5 mU/L was not associated with premature delivery, 1.9x and 2.5x increased risks of prematurity at <37 and <34 weeks, respectively, were observed among women with TSH >4.0 mU/L. Interestingly, this association no longer persisted after exclusion of TPOAb positive women or women with comorbidities. This shows that these factors may be important confounders in various studies and underlines the importance of performing in-depth analyses of observed associations.

The majority of large studies except one (293) focusing upon pre-eclampsia and hypertensive disorders, did not find associations of other pregnancy complications with elevated TSH (260,289,294). Mannisto and colleagues evaluated the relationship between pregnancy outcomes and thyroid function tests obtained at 12 weeks gestation in 5805 women. No adverse association between thyroid function and perinatal mortality was noted (294,295). A separate large study investigating the relationship between subclinical hypothyroidism and birth weight showed no effect on very low (<2500 g) or high (>4000 g) birth weights (289). This was also confirmed by Mannisto et al. (295). A recent meta-analysis broadly analyzed pregnancy outcomes in relation to maternal thyroid status (296). The authors found an increasing risk of pregnancy complications (pregnancy loss, preterm delivery and placental abruption) in relation

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to maternal subclinical hypothyroidism during early pregnancy, although subclinical hypothyroidism was variably defined across studies (296).

Together, despite some differences in study design, biochemical cut-offs applied, and slightly differing endpoints, the above studies overall indicate an increasing risk of pregnancy-specific complications, most notably pregnancy loss and preterm delivery, in relation to elevated maternal TSH concentrations. Importantly, however, this effect is exacerbated by the presence of elevated TPOAb, such that any additive risk is apparent in TPOAb positive women when TSH exceeds 2.5 mU/L. However, in TPOab negative women similar adverse risk is not consistently apparent until maternal TSH exceeds 5-10 mU/L.

Adverse Neurocognitive Effect on the Offspring

The detrimental effects of maternal thyroid hypofunction on fetal neurocognitive development are less clear. In support of an adverse impact attributable to maternal hypothyroidism, data from a large case-control study demonstrated a seven-point reduction in (IQ) among children born to untreated overtly hypothyroid women when compared to euthyroid controls (276). Findings also supported a delay in motor skill development, language development and attention at 7-9 years of age. Subsequent studies have shown similar impact on children born to women with isolated hypothyroxinemia, (19,283,297,298,299,300,301,302,303,304,314,317). Separately, three small studies analyzing only TPOAb positivity appear to similarly show an effect on neurocognitive outcome in the offspring but need to be confirmed in larger samples (199,201,305).

In contrast, the Controlled Antenatal Thyroid Screening (CATS) study was a large prospective, randomized controlled trial (RCT) investigating the benefit of population screening for elevated TSH concentrations and low FT4 concentrations in pregnant women. This study demonstrated no improvement in cognitive function when children of treated hypothyroid or hypothyroxinemic mothers were evaluated at three years of age. In this cohort, detection of either an elevated TSH or low freeT4 triggered initiation of 150 mcg/day LT4 therapy, at a mean of 13 weeks and 3 days gestation (306). Preliminary results of another large multicenter, randomized, controlled trial, the “Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy”, have recently become available. This study screened 97,226 pregnant women in order to randomize 677 women with subclinical hypothyroidism and 526 women with isolated maternal hypothyroxinemia to levothyroxine treatment vs. placebo at a mean time point of 17 weeks. Similarly, this study demonstrated no significant effect of treatment on offspring IQ at the age of five years (21). Other smaller studies support this conclusion (307,308,309).

Taken together, these prospective results provide insufficient evidence to conclude that treatment of subclinical hypothyroidism is associated with improved neurocognitive outcomes in offspring.

It should be noted, however, that the lack of positive data does not rule out a potential harmful effect, nor does it rule out the theoretical effectiveness of any intervention. It is important to note that such studies are highly difficult to complete, and often enroll subjects with

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great heterogeneity with regard to important study parameters. For example, the timing of levothyroxine intervention during gestation likely plays an important role in the effect of any intervention. The two randomized controlled studies described above initiated levothyroxine treatment only at the completion of the first trimester or later -- which may be too late to significantly impact neurodevelopment. Animal studies have suggested any window of opportunity is likely earlier in gestation (310,311). Similarly, the duration and severity of maternal hypothyroidism are likely important, yet virtually never controlled for, as all studies include only a single baseline measurement of TSH concentration during pregnancy. It therefore must again be emphasized that overt maternal hypothyroidism during pregnancy should be considered dangerous, and logic suggests that moderate (or even mild) maternal hypothyroidism may similarly impart risk. What remains uncertain is the nuanced understanding of how this risk is reduced or abated as the extent of maternal hypothyroidism is normalized, or other variables are modified. This point should be emphasized as we consider that the most common cause of maternal hypothyroidism has dramatically changed over the last century. Formerly, severe iodine deficiency was common, while more recently, the principal cause of maternal hypothyroidism is maternal Hashimoto's disease. These disorders are physiologically different, though both may impart a similar phenotype demonstrating elevated maternal TSH concentrations.

QUESTION 35 - WHAT ADVERSE OUTCOMES ARE ASSOCIATED WITH ISOLATED HYPOTHYROXINEMIA IN PREGNANCY?

Pop and colleagues initially reported a decrease in psychomotor test scores among offspring born to women with FT4 indices in the lowest 10th percentile (312), despite having normal serum TSH concentrations. Similarly, Li et al. (199) observed a reduction in IQ among offspring of mothers suffering from either hypothyroidism or isolated hypothyroxinemia during the first trimester. In recent years, additional prospective, non-randomized studies have similarly reported adverse child outcomes in children born to mothers with isolated hypothyroxinemia (19,192,193,259,279,280,281,282,283,284,287,288,289,291,294,295,306,313,314,318) (see **Table 5-6**). Adverse outcomes include lower IQ, language delay, worsened motor function, smaller head circumference, and an increased risk of autism. These data are derived from different populations across the world (China, Belgium, The Netherlands, Spain) with known differences in iodine status. In contrast to those studies investigating the association of elevated TSH concentrations with adverse pregnancy outcome, however, there are very few studies investigating isolated hypothyroxinemia and adverse pregnancy outcomes (see **Table 7**), excepting birth weight (314,315,316) and premature delivery (19). Available data suggest an association with higher birth weight and higher risk of premature delivery. Interestingly, many large-scale studies demonstrate that the populations of women with elevated TSH concentrations are generally exclusive from those identified with low freeT4 concentrations. For example, in the CATS study, approximately the same proportion of screened mothers were identified in the hypothyroxinemic and subclinically hypothyroid groups, with little overlap.

Overall, available evidence appears to show an association between hypothyroxinemia and cognitive development of the offspring, with uncertain effects on prematurity (314,315,316) and low birth weight (19). However, there exist no studies in which levothyroxine administration

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has been shown to ameliorate such harmful effects. In the CATS trial (303), 499 women were identified with low freeT4 concentrations, and 242 randomized to treatment with levothyroxine. This intervention failed to demonstrate any improvement in neurocognitive outcomes in the offspring at 3 years of age. However, women in this study received a fairly high dose (150 μg) of levothyroxine treatment and 10% needed a dose reduction because of biochemical or clinical signs of overtreatment. This is interesting, since a recent study by Korevaar et al. showed that both low and high free thyroxine concentrations may be associated with a decrease in child IQ and reduction of cerebral grey matter volume as assessed by MRI (317).

QUESTION 36 - SHOULD WOMEN WITH OVERT HYPOTHYROIDISM BE TREATED IN PREGNANCY?

As mentioned above, numerous retrospective and case-control studies confirm the detrimental effects of overt hypothyroidism on both pregnancy and fetal health (318). A recent retrospective study of > 1000 pregnant women on chronic levothyroxine replacement, showed that the risk of pregnancy loss increased proportionally to the degree of TSH elevation, with no increased risk associated with TSH normalization (318). Although no prospective, randomized investigation of levothyroxine intervention to improve obstetric outcomes or child development has occurred in pregnant women with overt hypothyroidism, such an investigation would be unethical to complete. Nonetheless, available data confirm the benefits of treating severe hypothyroidism during pregnancy.

- **Recommendation 27**
  Treatment of overt hypothyroidism is recommended during pregnancy. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 37- SHOULD WOMEN WITH SUBCLINICAL HYPOTHYROIDISM BE TREATED IN PREGNANCY?

Many prospective and retrospective studies have demonstrated an increased risk of pregnancy complications associated with mildly elevated maternal TSH concentrations, especially in TPOAb positive women. However, only a small number of studies have investigated the impact of LT4 treatment on pregnancy complications in such women.

As noted above, a single RCT has demonstrated a potential benefit of levothyroxine intervention at ~9 weeks gestation. Importantly, this study documented a reduction in the adverse pregnancy composite outcome only in TPOAb positive women with mild hypothyroidism (defined as a TSH >2.5 mU/L) (286). It should again be noted that the majority of women with subclinical hypothyroidism detected in this investigation were TPOAb negative, for whom no intervention or treatment was provided. This study also used a composite endpoint which included subjective endpoints such as Cesarean section rates and post-delivery admission to the NICU. Importantly, the authors' conclusion for their primary endpoint stated that universal screening for elevated TSH concentration in a broad population of pregnant women did not

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improve outcomes when compared to a high risk screening strategy. Outcomes of universal screening compared with no screening were not assessed.

A separate RCT demonstrated a decrease in preterm delivery and pregnancy loss in euthyroid (defined as TSH <4.2 mU/L) TPOAb positive women who were treated with levothyroxine beginning in the first trimester of pregnancy (28). However, the majority of pregnancy losses in the control group occurred before the average start of LT4 therapy.

Many studies have stratified the risk imparted by hypothyroidism according to TPOAb status, and consistently show that this risk is higher in TPOAb positive women (288). These data also suggest that the adverse impact associated with maternal TSH levels is apparent at lower TSH elevations in women known to be TPOAb positive compared to women who are TPOAb negative. Furthermore, two studies suggest a reduction in pregnancy loss when TPOAb positive women are treated with levothyroxine, even when biochemically euthyroid (28,180). Intervention trials have not been performed in TPOAb negative women.

However, despite the limitations of available interventional trials of levothyroxine therapy in this subclinically hypothyroid group, the data taken in aggregate appear to suggest a benefit of treatment, especially as it applies to reducing miscarriage in TPOAb positive women. Therefore, it seems reasonable to recommend or consider levothyroxine treatment for specific sub-groups of pregnant women with subclinical hypothyroidism. The strength of such recommendations, however, should differ depending on TPOAb status, as will the strength of evidence supporting treatment for each subgroup. This also necessitates that any pregnant women with an elevated TSH concentration must also be evaluated for TPOAb status. In making this recommendation, the task force acknowledges the very low risk inherent in initiating low-dose levothyroxine treatment. A dose of only 50 mcg daily is typically required for effective treatment of subclinically hypothyroid women.

- **Recommendation 28.**
  Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPO antibody status.

- **Recommendation 29**
  Subclinical hypothyroidism in pregnancy should be approached as follows:
  a) Levothyroxine therapy is recommended for:
  - TPO antibody positive women with a TSH greater than the pregnancy specific reference range (see Recommendation 1)
  (Strong recommendation, Moderate quality evidence)
  - TPO antibody negative women with a TSH greater than 10.0 mU/L.
  (Strong recommendation, Low quality evidence)
  b) Levothyroxine therapy may be considered for:
  - TPO antibody positive women with TSH concentrations > 2.5 mU/L and below the upper limit of the pregnancy specific reference range.
  (Weak recommendation, Moderate quality evidence)
  - TPO antibody negative women TPO antibody negative women with TSH concentrations greater than the pregnancy specific reference range and below 10.0 mU/L.

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(Weak recommendation, Low quality evidence)

c) Levothyroxine therapy is not recommended for:

- TPO antibody negative women with a normal TSH (TSH within the pregnancy specific reference range, or < 4.0 mU/L if unavailable).

(Strong recommendation, High quality evidence).

QUESTION 38 - SHOULD WOMEN WITH ISOLATED HYPOTHYROXINEMIA BE TREATED WITH LEVOTHYROXINE IN PREGNANCY?

Although several studies have reported adverse outcomes in children born to mothers with isolated hypothyroxinemia, no interventional data have yet been published that demonstrate beneficial effects of levothyroxine therapy. One observational study analyzing women at 12, 24, and 32 weeks of pregnancy demonstrated delayed infant neurodevelopment in women with persistent hypothyroxinemia. However, when FT4 concentrations increased during pregnancy, infant development was not adversely affected (312). Nevertheless, at present there are only two randomized, prospective, intervention trials in which women with a low FT4 were treated with levothyroxine, at 13 and 17 weeks gestation respectively (21,306). Both investigations failed to show any beneficial effect on cognitive development following levothyroxine administration, though a major limitation of the studies was the late timing of the intervention, after completion of the first trimester. Nevertheless, given the existing interventional data, treatment of isolated hypothyroxinemia cannot be recommended at this time.

- **Recommendation 30**
  Isolated hypothyroxinemia should not be routinely treated in pregnancy. ***(Weak recommendation, Low quality evidence)***

QUESTION 39- WHAT IS THE OPTIMAL METHOD OF TREATING HYPOTHYROIDISM IN PREGNANT WOMEN?

Delivery of T4 is crucial for the developing fetal brain (313). The ratio of T4 to T3 in desiccated thyroid preparations is 4.2:1, which is significantly lower than the 14:1 ratio of secretion by the human thyroid gland. This relative excess of T3 leads to supraphysiologic maternal levels of T3 and relatively low levels of T4 (319). Patients using either desiccated thyroid or a treatment regimen combining T3 and T4 (320) are likely at risk for having insufficient transfer of maternal T4 to the fetal brain. It is notable that the majority of fetal T3 present in the central nervous system (CNS) during pregnancy is derived from maternal T4 actively transported into this space. The fetal CNS is relatively impermeable to T3, which therefore argues against use of exogenous T3 during pregnancy. For these reasons, the task force feels that any T3 containing preparation should be avoided for the treatment of maternal hypothyroidism during pregnancy.

- **Recommendation 31**
  The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. Other thyroid preparations such as triiodothyronine (T3) or desiccated thyroid should not be used in pregnancy. ***(Strong recommendation, Low quality evidence)***

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QUESTION 40- WHAT IS THE BIOCHEMICAL GOAL WHEN TREATING HYPOTHYROIDISM IN PREGNANT WOMEN?

- **Recommendation 32**
  In parallel to the treatment of hypothyroidism in a general population, it is reasonable to target a TSH in the lower half of the trimester specific reference range. When this is not available, it is reasonable to target maternal TSH concentrations below 2.5 mU/L. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 41 - ARE THERE CIRCUMSTANCES WHERE EUTHYROID WOMEN ARE AT RISK FOR HYPOTHYROIDISM ONCE PREGNANT?

In 1994, Glinoer et al. performed a prospective study in 87 euthyroid, TPOAb positive women evaluated before and during early pregnancy (147). Twenty percent of women in the study developed a TSH > 4 mU/L during gestation despite a normal TSH and no requirement for levothyroxine prenatally. This occurred despite the expected decrease in TPOAb titers during pregnancy (147). Negro et al. demonstrated similar results in a prospective study (28). The authors found that in TPOAb positive euthyroid women, TSH levels increased progressively as gestation progressed, from a mean of 1.7 mU/L (12th week) to 3.5 mU/L (term), with 19% of women having a supra-normal TSH concentration at delivery. These findings confirm that an increased requirement for thyroid hormone occurs during gestation. In women who are TPOAb positive, both overt and subclinical hypothyroidism may occur due to a lack of ability of the thyroid to augment production when needed during pregnancy. Similarly, patients who undergo hemithyroidectomy or receive radioactive iodine and are euthyroid before pregnancy are at risk for developing elevated serum TSH levels during gestation.

In summary, euthyroid patients who are anti-thyroid Ab positive, post-hemithyroidectomy or treated with radioactive iodine, have an increased propensity for the development of hypothyroidism in gestation, and should be monitored regularly.

QUESTION 42- HOW SHOULD WOMEN WITH HYPOTHYROIDISM, OR AT RISK FOR HYPOTHYROIDISM, BE MONITORED THROUGH PREGNANCY?

In women at risk for hypothyroidism (TPO or TGAb positive, post-hemithyroidectomy, and/or post-radioactive iodine) increased surveillance is recommended. Based on findings extrapolated from investigations of treated hypothyroid women from early pregnancy onwards (321), it is reasonable to evaluate these women for TSH elevation approximately every 4 weeks during pregnancy. Serial testing is preferably continued through mid-pregnancy, as the increased thyroxine demand continues throughout the first half of gestation.

A study by Yassa and colleagues investigated the optimal timing of subsequent assessment of thyroid function following dose modification (322) though this was in patients consuming levothyroxine prenatally, and may not be generalizable to patients not taking levothyroxine but at risk for hypothyroidism.

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- **Recommendation 33**
  Women with overt and subclinical hypothyroidism (treated or untreated), or those at risk for hypothyroidism (e.g. patients who are euthyroid but TPO or TGAb positive, post-hemithyroidectomy, or treated with radioactive iodine) should be monitored with a serum TSH measurement approximately every 4 weeks until mid-gestation, and at least once near 30 weeks gestation. ***(Strong recommendation, High quality evidence)***

QUESTION 43 - HOW DO TREATED HYPOTHYROID WOMEN (RECEIVING LEVOTHYROXINE) DIFFER FROM OTHER PATIENTS DURING PREGNANCY? WHAT CHANGES CAN BE ANTICIPATED IN SUCH PATIENTS DURING GESTATION?

The major physiologic thyroid changes during pregnancy have been thoroughly studied. Total body thyroxine requirements are not static throughout gestation. Rather, data demonstrate that the total body thyroxine pool must increase by ~40-50% to maintain a euthyroid state (321,323). In a healthy woman who becomes pregnant, the pregnancy hormone hCG plays a major role as a stimulus of maternal thyroid hormone production, especially throughout the first half of pregnancy. Together with pituitary TSH, placental hCG stimulates endogenous thyroid hormone production when an intact thyroid is present, and helps to maintain a euthyroid state during gestation.

In women with known hypothyroidism, serum hCG and TSH cannot stimulate adequate thyroxine production. If exogenous levothyroxine is not adjusted, the increased demand of pregnancy will outstrip supply, and maternal hypothyroidism will occur. Clinical studies have confirmed that the increased requirement for thyroxine (or exogenous levothyroxine) occurs as early as 4-6 weeks of pregnancy (321). Such requirements gradually increase through 16-20 weeks of pregnancy, and thereafter plateau until the time of delivery. These data provide the basis for recommending adjustments of LT4 dosage when affected women become pregnant and also for the timing of follow-up intervals for TSH in treated patients.

QUESTION 44 - WHAT PROPORTION OF TREATED HYPOTHYROID WOMEN (RECEIVING LEVOTHYROXINE PRENATALLY) REQUIRE CHANGES IN THEIR LEVOTHYROXINE DOSE DURING PREGNANCY?

Between 50 and 85% of LT4-treated hypothyroid women need to increase exogenous levothyroxine dosing during pregnancy (277,321,323). The incremental increase largely depends on the underlying etiology of the hypothyroidism. There is a greater likelihood that dose increases will be required in those patients without functional thyroid tissue (e.g. due to radioablation or surgery, etc) in comparison to patients with Hashimoto's thyroiditis (324,325). The preconception level of TSH as well as other factors can also influence the rapidity and extent of LT4 augmentation necessary to maintain a euthyroid state during pregnancy. For example,

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variation and changes in maternal estrogen levels during pregnancy correlate with variations in the gestational requirements for LT4 (321).

The levothyroxine adjustment should be made as soon as possible after pregnancy is confirmed to reduce the probability of hypothyroidism. Normalization of TSH concentrations throughout gestation is the goal. For women receiving LT4 preconception, a prospective, randomized study has provided evidence that supports a single dose-adjustment strategy rather than a stepwise approach for LT4 dosage adjustment postconception (322). For euthyroid women receiving once-daily dosing of LT4 (regardless of the dosage), a recommendation to increase by 2 additional tablets weekly (9 tablets per week instead of 7 tablets per week, giving a 29% increase) can effectively mimic gestational physiology and thus prevent maternal hypothyroidism during the first trimester (322). Another option is to increase the dosage of daily levothyroxine by approximately 25-30%. Dosage augmentation should occur as soon as possible when a missed menstrual cycle or suspected pregnancy occurs, and this should be discussed with every patient in the pre-pregnancy setting. Confirmatory biochemical testing should also occur simultaneously.

QUESTION 45 - HOW SHOULD PRECONCEPTION LEVOTHYROXINE BE ADJUSTED IN TREATED HYPOTHYROID WOMEN (RECEIVING LEVOTHYROXINE) PLANNING PREGNANCY?

The difficulties inherent to achieving rapid, postconceptional TSH normalization have also focused attention upon pre-conception TSH modulation. Different cut-off values for preconception TSH, ranging from <1.2 to <2.5 mU/L have been advocated. In one study, only 17% of women with TSH <1.2 mU/L had to increase LT4 dose later during pregnancy (326). Given this, it is recommended that all treated hypothyroid women (currently receiving levothyroxine) optimize thyroid parameters pre-conception. A maternal serum TSH concentration <2.5 mU/L is a reasonable goal for such women. Even lower preconception TSH values (<1.5 mU/L) could reduce the risk of TSH elevation during the 1st trimester (322), but a lower treatment target may not improve outcomes as the LT4 dose can be immediately increased upon a positive pregnancy test. Furthermore, the process of achieving a TSH concentration at the lower end of the reference range could induce sub-normal TSH concentrations in some patients. Though generally safe for any developing fetus, potential such effects upon conception and/or successful implantation are unknown.

- **Recommendation 34**
  Treated hypothyroid women of reproductive age should be counseled regarding the likelihood of increased demand for levothyroxine during pregnancy. Such women should also be counseled to contact their caregiver immediately upon a confirmed or suspected pregnancy. (***Strong recommendation, High quality evidence***)

- **Recommendation 35**
  In hypothyroid women treated with levothyroxine who are planning pregnancy, serum TSH should be evaluated preconception, and levothyroxine dose adjusted to achieve a TSH value

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between the lower reference limit and 2.5 mU/L. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 36**
  Hypothyroid patients receiving LT4 treatment with a suspected or confirmed pregnancy (e.g. positive home pregnancy test) should independently increase their dose of LT4 by ~20-30% and urgently notify their caregiver for prompt testing and further evaluation. One means of accomplishing this is to administer 2 additional tablets weekly of the patient's current daily levothyroxine dosage. ***(Strong recommendation, High quality evidence)***

QUESTION 46 - HOW SHOULD LT4 BE ADJUSTED POSTPARTUM?

The increased LT4 dose requirements during gestation are a function of pregnancy itself. Therefore, following delivery, maternal LT4 dosing should be reduced to prepregnancy levels, and a serum TSH assessed 6 weeks thereafter. However, a study demonstrated that more than 50% of women with Hashimoto's thyroiditis required an increase in the pregestational thyroid hormone dose in the postpartum period, presumably due an exacerbation of autoimmune thyroid dysfunction postpartum (327). In women started on LT4 during pregnancy for thyroid autoimmunity in the absence of TSH elevation, the LT4 can be stopped at delivery, with serum TSH assessment at 6 weeks postpartum.

- **Recommendation 37**
  Following delivery, LT4 should be reduced to the patient's preconception dose. Additional thyroid function testing should be performed at approximately 6 weeks postpartum. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 38**
  Some women in whom LT4 is initiated during pregnancy may not require LT4 postpartum. Such women are candidates for discontinuing LT4, especially when the LT4 dose is ≤50 mcg daily. The decision to discontinue LT4, if desired, should be made by the patient and their caregiver. If LT4 is discontinued, serum TSH should be evaluated in ~ 6 weeks. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 47 - WHAT IS THE OUTCOME AND LONG-TERM PROGNOSIS WHEN MATERNAL HYPOTHYROIDISM IS EFFECTIVELY TREATED THROUGH GESTATION?

Although untreated (or incompletely treated) hypothyroidism can adversely affect pregnancy, there are no data to suggest that women with adequately treated subclinical or overt hypothyroidism have an increased risk of any obstetrical complication. Consequently, there is no indication for any additional obstetric testing or surveillance in pregnancies of women with either subclinical or overt hypothyroidism who are being monitored and treated appropriately.

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QUESTION 48 - EXCEPT FOR MEASUREMENT OF MATERNAL THYROID FUNCTION, SHOULD ADDITIONAL MATERNAL OR FETAL TESTING OCCUR IN TREATED, HYPOTHYROID WOMEN DURING PREGNANCY?

- **Recommendation 39**
  In the care of women with adequately treated hypothyroidism, no other maternal or fetal testing (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) is recommended beyond measurement of maternal thyroid function unless needed due to other circumstances of pregnancy. An exception to this is women with Graves' disease effectively treated with ^{131}I ablation or surgical resection, who require TRAb monitoring. ***(Strong recommendation, Moderate quality evidence)***

VIII. Thyrotoxicosis in Pregnancy

QUESTION 49 - WHAT ARE THE CAUSES OF THYROTOXICOSIS IN PREGNANCY?

Thyrotoxicosis is the clinical syndrome of hypermetabolism and hyperactivity that results when a person is exposed to supraphysiological amounts of thyroid hormones. The most common cause of thyrotoxicosis is hyperfunction of the thyroid gland (hyperthyroidism), and the most common cause of hyperthyroidism in women of childbearing age is autoimmune Graves' disease (GD) occurring before pregnancy in 0.4-1.0 % of women and in approximately 0.2 % during pregnancy (328).

Less common non-autoimmune causes of hyperthyroidism in pregnancy include toxic multinodular goiter and toxic adenoma. Subacute painful or painless thyroiditis with passive release of thyroid hormones from a damaged thyroid gland are less common causes of thyrotoxicosis in pregnancy, and a number of other conditions such as a TSH-secreting pituitary adenoma (329), struma ovarii (330), functional thyroid cancer metastases, or germline TSH receptor mutations (331) are very rare. A special cause of thyrotoxicosis is overtreatment with or factitious intake of thyroid hormone.

More frequent than GD as the cause of thyroid function tests demonstrating hyperthyroxinemia is 'gestational transient thyrotoxicosis', which is limited to the first half of pregnancy. This condition, characterized by elevated FT4 and suppressed serum TSH, is diagnosed in about 1-3% of pregnancies. This frequency depends on the geographic area and is secondary to elevated hCG levels (332,333). Often it is associated with hyperemesis gravidarum, defined as severe nausea and vomiting in early pregnancy with more than 5% weight loss, dehydration, and ketonuria. Hyperemesis gravidarum occurs in 3-10 per 1000 pregnancies (334,335). Other conditions associated with hCG-induced thyrotoxicosis include multiple gestation, hydatidiform mole, and choriocarcinoma (336,337). Most cases present with marked elevations of serum hCG (14). A TSH receptor mutation leading to functional hypersensitivity to hCG also has been recognized as a rare cause of pregnancy-associated hyperthyroidism (338).

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QUESTION 50 - WHAT IS THE APPROPRIATE INITIAL EVALUATION OF A SUPPRESSED SERUM TSH CONCENTRATION DURING THE FIRST TRIMESTER OF PREGNANCY?

Serum TSH may decrease in the first trimester of normal pregnancy as a physiological response to the stimulating effect of hCG upon the TSH receptor. A peak hCG level typically occurs between 7-11 weeks gestation (339). In particular, a serum TSH below 0.1 mU/L (in some cases even undetectable) may be present in approximately 5 % of women by week 11 of pregnancy (270). Any subnormal serum TSH value should be evaluated in conjunction with serum TT4 (or FT4) and T3 values. The biochemical diagnosis of overt hyperthyroidism is confirmed in the presence of a suppressed or undetectable serum TSH and inappropriately elevated serum TT4/FT4, or T3 (Section III).

QUESTION 51 - HOW CAN GESTATIONAL TRANSIENT THYROTOXICOSIS BE DIFFERENTIATED FROM GRAVES' HYPERTHYROIDISM IN PREGNANCY?

Diagnosing the cause of the disease is essential in any patient with thyrotoxicosis. In early pregnancy, the differential diagnosis in the majority of cases is between Graves' hyperthyroidism and gestational transient thyrotoxicosis (332,333). In both situations, common clinical manifestations include palpitations, anxiety, tremor, and heat intolerance. A careful history and physical examination is of utmost importance in establishing the etiology. The findings of no prior history of thyroid disease, no stigmata of Graves' disease (goiter, orbitopathy), a self-limited mild disorder, and symptoms of emesis favor the diagnosis of gestational transient thyrotoxicosis.

If other causes for thyrotoxicosis are suspected, measurement of TSH receptor antibody (TRAb) is indicated. If this is negative or thyroid nodules are suspected based on clinical examination, a thyroid ultrasound should be performed to evaluate nodularity. Serum hCG is, on average, higher in gestational transient thyrotoxicosis than in patients with GD, but overlap is considerable and the clinical usefulness of such measurement is limited (340). No study has demonstrated usefulness of thyroid ultrasonography for differentiating between gestational transient thyrotoxicosis and GD. In the presence of a nodular goiter, a serum Total T3 determination is helpful in assessing the possibility of the "T3 Toxicosis" syndrome. Total T3 determination may also be of benefit in diagnosing T3 thyrotoxicosis caused by GD. In general, serum T3 tends to be disproportionately elevated more than T4 in cases of thyrotoxicosis caused by direct thyroid hyperactivity. In comparison, T4 tends to be disproportionately elevated beyond T3 when thyrotoxicosis is caused by destructive processes such as thyroiditis (341).

- **Recommendation 40**
  When a suppressed serum TSH is detected in the first trimester (TSH less than the reference range), a medical history, physical examination, and measurement of maternal serum Free T4 or total T4 concentrations should be performed. Measurement of TSH receptor antibodies (TRAb), and maternal total T3, may prove helpful in clarifying the etiology of thyrotoxicosis. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 41**

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Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy. ***(Strong recommendation, High quality evidence)***

QUESTION 52 - WHAT IS THE APPROPRIATE MANAGEMENT OF GESTATIONAL TRANSIENT THYROTOXICOSIS?

The management of women with gestational transient thyrotoxicosis depends on the severity of symptoms. In women with hyperemesis gravidarum, control of vomiting and treatment of dehydration with intravenous fluids is the customary treatment. Women with severe hyperemesis gravidarum need frequent medical visits for management of dehydration and electrolyte abnormalities. In some cases, hospitalization is required. Antithyroid drugs (ATDs) are not indicated, since the serum T4 returns to normal by 14-18 weeks gestation and ATD use in early pregnancy increases risk of birth defects. Importantly, obstetrical outcome was not improved in isolated cases in which gestational transient thyrotoxicosis was treated with ATDs (342). However, there are no studies reported in the literature comparing ATD therapy vs. supportive therapy. In situations where symptomatic therapy is indicated, small amounts of beta-blockers given over a limited time period may be useful, and close follow-up with repeat investigation for the cause of disease should be performed.

- **Recommendation 42**
  The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. Antithyroid drugs are not recommended, though beta-blockers may be considered. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 53 - HOW SHOULD WOMEN WITH GRAVES' DISEASE SEEKING FUTURE PREGNANCY BE COUNSELED?

The planning of therapy in relation to possible future pregnancy should be discussed with all women of childbearing age who develop thyrotoxicosis. In general, pregnancy should be postponed until a stable, euthyroid state is reached. As a guide, two sets of thyroid function test within the reference range, at least one month apart, and with no change in therapy between tests, can be used to define 'a stable euthyroid state'. The use of contraception until the disease is controlled is strongly recommended.

A hyperthyroid patient who desires future pregnancy may be offered ablative therapy using ^{131}I, thyroid surgery, or medical therapy. Each therapeutic option carries advantages and disadvantages, as detailed below (see **Table 8**). This is further discussed in the ATA guidelines for the management of thyrotoxicosis (343).

Ablative Therapy

If the patient opts for radioactive iodine ablative therapy prior to pregnancy, the following recommendations should be provided: 1) TRAb levels tend to increase following ^{131}I therapy and may remain elevated for many months following ^{131}I therapy. Therefore, patients

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with high TRAb levels or severe hyperthyroidism may favor consideration of other therapeutic options such as surgery (344); 2) a subset of young patients with severe GD may not become stably euthyroid within the first year after ^{131}I therapy (345,346,347,348). 3) If ^{131}I therapy is planned, a pregnancy test should be performed 48 hours before ^{131}I ablation to confirm absence of unexpected pregnancy; and 4) conception should be delayed 6 months and until a stable euthyroid state is reached after ablation and initiation of L-T4 replacement therapy.

Antithyroid Drugs

If the patient chooses ATD therapy, the following recommendations should be given:

1) The increased risk of birth defects associated with both PTU and MMI use during early pregnancy should be reviewed; 2) If possible, ATDs should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored. 3) Consideration can be given to discontinuing PTU after the first trimester and switching to MMI in order to decrease the risk of liver failure in the mother.

- **Recommendation 43**
  In all women of childbearing age who are thyrotoxic, the possibility of future pregnancy should be discussed. Women with Graves' disease seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation, including the association of birth defects with antithyroid drug use. Preconception counseling should review the risks and benefits of all treatment options, and the patient's desired timeline to conception. **(*Strong recommendation, High quality evidence)***

- **Recommendation 44**
  Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy. Several treatment options exist, each of which are associated with risks and benefits. These include ^{131}I ablation, surgical thyroidectomy, or ATD therapy. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 54 - WHAT IS THE MANAGEMENT OF PATIENTS WITH GRAVES' HYPERTHYROIDISM DURING PREGNANCY?

Several studies have shown that obstetric and medical complications are directly related to control of maternal hyperthyroidism, and the duration of the euthyroid state throughout pregnancy (339,342,344,349). Poor control of thyrotoxicosis is associated with pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure (350). Moreover, some studies suggest fetal exposure to excessive levels of maternal thyroid hormone may program the offspring to develop diseases such as seizure disorders and neurobehavioral disorders in later life (351).

Thionamide antithyroid drugs (MMI, carbimazole (CM), and PTU) are the mainstay of treatment for hyperthyroidism during pregnancy (352,353). They reduce iodine organification and coupling of monoiodotyrosine and diiodotyrosine, therefore inhibiting thyroid hormone

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synthesis. Because the block is not absolute and the thyroid contains a depot of thyroid hormone bound to thyroglobulin, the normalization of thyroid function tests takes place gradually over weeks. The initial dose of ATD depends on the severity of the symptoms and the degree of hyperthyroxinemia. In general, initial doses of ATDs during pregnancy are as follows; MMI 5-30 mg daily (typical dose in average patient 10-20 mg), CM 10-40 mg daily and PTU 100-600 mg daily (typical PTU dose in average patient 200-400 mg per day). The equivalent potency of MMI to PTU is approximately 1:20 (e.g. 5 mg MMI = 100 mg of PTU) (354,355,356). Ten mg of CM is rapidly metabolized to approximately 6 mg MMI (328). Because the half-life of PTU is shorter than that of MMI, PTU dosing should generally be split into 2 or 3 daily doses. In comparison, MMI can generally be given in one daily dose. In rare cases of severe hyperthyroidism, twice or three-times daily dosing may be of benefit (357,358).

Importantly, side effects occur in 3-5% of patients taking thionamide drugs, the majority of which are allergic reactions such as skin rash (352), whereas the severe side effects of agranulocytosis (0.15%) (359,360) and liver failure (<0.1%) (92) are rare. Most side effects develop within the first months following initiation (359) or re-initiation (361) of therapy. In 2010 the U.S.Food and Drug Association (FDA) called attention to the risk of hepatotoxicity in patients exposed to PTU, because PTU had been found to be third on the list of drugs leading to liver transplantation in the U.S. (362,363). An advisory committee recommended limiting the use of PTU to the first trimester of pregnancy (364). Exceptions to this are patients with MMI allergy or those with thyroid storm. Monitoring hepatic enzymes during administration of PTU may be considered. However, no prospective data exist which have demonstrated that the monitoring of liver enzymes is effective in preventing fulminant PTU-induced hepatotoxicity.

However, the greatest risk surrounding the use of ATDs in pregnancy is related to their potential teratogenic effects (365). As early as 1972 exposure to MMI has been associated with aplasia cutis (366). Subsequently, several other types of congenital malformations have been associated with MMI use. A ‘syndrome of methimazole/carbimazole embryopathy’ was described, that also includes dysmorphic facies (367, 368). Apart from aplasia cutis, defects with a statistically significant association with the use of MMI include choanal or esophageal atresia, various types of abdominal wall defects including umbilicocele, eye, urinary system, and ventricular septal defects (369,370,371). Recent studies have shown that these complications are more common than previously thought, and they affect 2-4 % of children who have been exposed to MMI in early pregnancy, especially during gestational weeks 6-10 (369,370,372).

PTU was previously considered a safe medication for use during gestation (367,364). Recently, however, a Danish study revealed that 2-3% of children exposed to PTU developed birth defects associated with this therapy (370). The defects were primarily face and neck cysts (often considered to be ‘minor birth defects’) and urinary tract abnormalities (in males). Previous to the recent investigation, such abnormalities were not commonly associated with PTU exposure, likely because they were diagnosed later in life when complications ensued. Importantly, however, most affected patients received surgery for the abnormality (373). Thus, PTU associated birth defects appear less severe than MMI associated birth defects, but occur with similar incidence.

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Beta adrenergic blocking agents, such as propranolol 10-40 mg every 6-8 hours may be used for controlling hyper-metabolic symptoms until patients have become euthyroid on ATD therapy. The dose should be reduced as clinically indicated. In the vast majority of cases the drug can be discontinued in 2 to 6 weeks. Long-term treatment with beta-blockers has been associated with intrauterine growth restriction, fetal bradycardia and neonatal hypoglycemia (374). One study suggested a higher rate of spontaneous pregnancy loss when both drugs were taken together, as compared to patients receiving only MMI (375). However, it was not clear that this difference was attributable to the medication as opposed to the underlying condition. Beta-blocking drugs may be used as preparation for thyroidectomy.

QUESTION 55 - SHOULD ANTITHYROID MEDICATION BE WITHDRAWN OR MODIFIED IN EARLY PREGNANCY?

Many patients receiving ATD therapy for GD gradually enter remission of the autoimmune abnormality when made euthyroid. Though approximately half of patients eventually experience a relapse of hyperthyroidism when the antithyroid medication is withdrawn after 1-2 years of therapy, only a small fraction of patients who have become TRAb negative during therapy will become hyperthyroid within the first months. In support of this, in a prospective Norwegian study of 218 GD patients treated with ATD for 12 months, only 5% of TRAb negative patients became hyperthyroid within 8 weeks after ATD withdrawal (376).

Thus, one option when pregnancy is diagnosed in a woman receiving ATD therapy for GD and who, based on clinical and biochemical findings appears to be in remission, is to withdraw ATD medication and perform repeated thyroid function testing during the first trimester of pregnancy. If ATD therapy is needed during the first trimester, PTU is preferred over MMI because the risk for severe birth defects is lower. Cessation of medication has to be recommended early in gestation, before the major teratogenic periods (gestational weeks 6-10) (372,373,376,377).

Gestational weeks are calculated from the first day of the last normal menstrual period, and at week 5 when the next normal menstruation does not appear in a pregnant woman. Sensitive pregnancy tests are widely available and should detect pregnancy by this time. Optimally, women receiving ATD should test for pregnancy within the first days of a missing or unusually weak menstruation. If the test is positive, the woman should contact the caregiver responsible for thyroid therapy to receive instruction regarding withdrawing or modifying ATD therapy, and to discuss thyroid function testing.

The risk of rapid relapse of hyperthyroidism after medication withdrawal in early pregnancy varies among patients. The risk is high in patients who have been treated for a short period (< 6 months), who have suppressed or low serum TSH while on medication pre-pregnancy, who require >5-10 mg of MMI per day to stay euthyroid, who have active orbitopathy or large goiter, and those who have high levels of TRAb (378). As this assessment is based upon clinical judgment, no specific single parameter may be used to assign risk. However, if the risk is considered high, medication should not be withdrawn, and PTU should be administered as the drug of choice.

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Even if conventional ATDs are effective in achieving a euthyroid state, the risk of birth defects has raised the question of alternative types of drug therapy for hyperthyroidism. Iodine in pharmacological doses was widely used to treat hyperthyroidism before the thionamide drugs (and radioiodine) became available. It was (and is) especially effective as a preparation for subsequent thyroid surgery, as introduced by Plummer in 1923 (379). However, escape from the effect during prolonged therapy was not uncommon, especially in patients with severe hyperthyroidism (380) and iodine therapy is now mostly used to reduce thyroid blood flow before surgery, and as part of the combination of therapies given to patients with thyrotoxic crises.

An exception to this narrow indication for the treatment of hyperthyroidism is Japan, where there is considerable experience with high-dose iodine therapy in pregnancy (381,382). The doses of iodine used have varied between 5 and 75 mg per day, adjusted according to thyroid function tests. In a recent retrospective non-randomized study, substituting MMI with potassium iodine in early pregnancy reduced the risk of birth defects. However, a proportion of such pregnant women became hyperthyroid following the change in treatment (382). Important to note, Japan is a high iodine intake country, and the Japanese results may not be reproducible in other countries. Cases of iodine-induced congenital hypothyroidism have been reported in children of U.S. women treated with high-dose iodine during pregnancy (383), and the use of iodine containing disinfectants during labor is a well established cause of elevated TSH during screening for congenital hypothyroidism (384). Thus, at present, such therapy cannot be recommended outside Japan until more evidence on safety and efficacy is available.

Theoretically, other possible treatments can also be considered. Cholestyramine is not absorbed from the gut (and thus not transferred to the fetus), and may moderately reduce circulating thyroid hormones by binding the hormones during their entero-hepatic circulation (385,386,387). Cholestyramine has been used in pregnancy to treat obstetric cholestasis (388). Gastrointestinal discomfort with nausea, vomiting, and diarrhea may be a problem (388), and there is a risk of binding in the gut of vitamins and other substances important in pregnancy. Perchlorate competitively inhibits the active transport of iodide into the thyroid (and into breast milk), and it has been used to treat hyperthyroidism (389,390). Limited evidence suggests it has no teratogenic effects as long as normal maternal thyroid function is maintained (391). In summary, more data are needed before the use of any such drugs can be recommended. Lithium has thyroid-inhibiting effects somewhat similar to pharmacological doses of iodine (392) but may be teratogenic (393), and therefore should not be used to treat hyperthyroidism in pregnancy.

- **Recommendation 45**
  Women taking MMI or PTU should be instructed to confirm potential pregnancy as soon as possible. If the pregnancy test is positive, pregnant women should contact their caregiver immediately. ***(Strong recommendation, High quality evidence)***

- **Recommendation 46**
  a. In a newly-pregnant woman with Graves' disease, who is euthyroid on a low dose of MMI (≤5-10 mg/day) or PTU (≤ 100-200 mg/day), the physician should consider discontinuing all antithyroid medication given potential teratogenic effects. The decision to stop medication

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should take into account the disease history, goiter size, duration of therapy, results of recent thyroid function tests, TRAb measurement, and other clinical factors. ***(Weak recommendation, Low quality evidence)***

b. Following cessation of antithyroid medication, maternal thyroid function testing (TSH, and FT4 or TT4) and clinical examination should be performed every 1-2 weeks to assess maternal and fetal thyroid status. If the pregnant woman remains clinically and biochemically euthyroid, test intervals may be extended to 2-4 weeks during the 2nd and 3rd trimester. ***(Weak recommendation, Low quality evidence)***

c. At each assessment, the decision to continue conservative management (withholding antithyroid medication) should be guided both by the clinical and the biochemical assessment of maternal thyroid status. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 47**

In pregnant women with a high risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, continued antithyroid medication may be necessary. Factors predicting high clinical risk include being currently hyperthyroid, or requirement of> 5-10 mg/day MMI or > 100-200 mg/day PTU to maintain a euthyroid state. In such cases:

a. PTU is recommended for the treatment of maternal hyperthyroidism through 16 weeks of pregnancy. ***(Strong recommendation, Moderate quality evidence)***

b. Pregnant women receiving MMI who are in need of continuing therapy during pregnancy should be switched to PTU as early as possible. ***(Weak Recommendation, Low quality evidence)***

c. When shifting from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g. MMI 5 mg daily = PTU 100 mg twice daily). ***(Strong recommendation, Moderate quality evidence)***

d. If ATD therapy is required after 16 weeks gestation, it remains unclear whether PTU should be continued or therapy changed to MMI. As both medications are associated with potential adverse effects and shifting potentially may lead to a period of less-tight control, no recommendation regarding switching antithyroid drug medication can be made at this time. ***(No recommendation, Insufficient evidence)***

QUESTION 56 –WHAT ARE THE PRINCIPLES OF THYROID TESTING AND ANTITHYROID MEDICATION ADMINISTRATION WHEN TREATING GRAVES' HYPERTHYROIDISM DURING PREGNANCY?

Thyroid stimulating antibodies, antithyroid drugs, and most maternal thyroid hormones can effectively cross the placenta barrier. When the fetal thyroid is functional, it can respond to TRAb antibodies, causing excess fetal production of thyroid hormone. Furthermore, if the mother has an intact thyroid and is hyperthyroid from GD, the fetus will also be exposed to the hyperthyroxinemia produced by the mother's thyroid during gestation. Typically, fetal hyperthyroidism due to cross-placental passage of TRAb develops at or after week 20 of pregnancy. However, one case has been published in which excessive maternal TRAb production led to fetal hyperthyroidism by week 18 (394).

As mentioned, MMI, PTU, and CM also effectively cross the placenta, and therefore ATD therapy for maternal hyperthyroidism also modulates fetal thyroid function. Importantly,

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all antithyroid drugs tend to be more potent in the fetus than in the mother. Thus, when the mother is made euthyroid, the fetus is often overtreated (395). Therefore, in order to avoid a deleterious fetal impact, the aim of treatment is to maintain maternal TT4/FT4 values at, or just above the pregnancy-specific upper limit of normal. As a general rule, the smallest possible dose of ATDs should be used whenever possible.

In the setting of hyperthyroidism during pregnancy, maternal TT4/FT4 and TSH (and in cases of severe hyperthyroidism, also serum T3) should be measured approximately every 2-4 weeks following initiation of therapy, and every 4-6 weeks after achieving the target value (396,397,398). When trimester-specific FT4 values are not available, use of the reference range for non-pregnant patients is recommended. Separately, a total T4 measurement with reference value 1.5 times the non-pregnancy range may be used in 2nd and 3rd trimesters. Over-treatment should be avoided, because of the possibility of inducing fetal goiter and or fetal hypothyroidism (399).

In the first trimester of pregnancy some women with GD experience an exacerbation of symptoms (400), which is parallel to the moderate increase in incidence of GD in early pregnancy (401). By the 3rd trimester the incidence of GD becomes very low (401) corresponding to the general decrease in thyroid autoimmunity, with a decrease in TRAb.

Discontinuation of all ATD therapy is feasible in 20-30% of patients in the last trimester of gestation (402). Maternal serum TSH well within the reference range is a sign that the ATD dose has to be reduced to avoid fetal overtreatment. If this is not done, fetal hypothyroidism and goiter may develop from overtreatment with ATDs. Disappearance of maternal TRAb in late pregnancy indicates a high likelihood of successful ATD withdrawal.

- **Recommendation 48**
  a. In women being treated with antithyroid drugs in pregnancy, FT4/TT4 and TSH should be monitored approximately every 4 weeks. ***(Strong recommendation, Moderate quality evidence)***
  b. Antithyroid medication during pregnancy should be administered at the lowest effective dose of MMI or PTU, targeting maternal serum FT4/TT4 at or moderately above the reference range. ***(Strong recommendation, High quality evidence)***

Because the fetal thyroid responds more strongly to ATD therapy than the maternal thyroid, mothers on an antithyroid drug in the second half of pregnancy, who by non-pregnancy standards would be considered euthyroid, should have the antithyroid drug dose reduced to protect the fetus.

In occasional patients, GD stays very active and serum TT3 may remain elevated even if TT4/FT4 becomes normal or even low (403). An increase in ATD dose to normalize maternal serum TT3 will cause elevated serum TSH in the infants at birth (398), and a balance in ATD dosing with careful clinical evaluation of the fetus and the mother is needed.

Worsening of disease activity with a need for an increase in ATD dose or relapse of previously remitted disease often occurs after delivery (400,404). Women should be informed

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about this risk, and appropriate monitoring performed. A single Japanese study has suggested that relapse may be prevented by low-dose ATD during the postpartum period (405), but more studies on this are needed.

The combination of LT4 and an ATD ('block-replace therapy') has in general been shown not to improve GD remission rates (406), and it results in a larger dose of ATD required in order to maintain the FT4 within the target range. The placenta is readily permeable to the ATD but not to the LT4 given to the mother, and the fetal thyroid is relatively more sensitive to the effect of ATDs than the maternal thyroid. Therefore, block-replacement therapy given to the mother in the second half of pregnancy will generally lead to fetal goiter and hypothyroidism (403). The only indication for such combination therapy during pregnancy is in the treatment of isolated fetal hyperthyroidism caused by maternal TRAb production in a mother who previously received ablative therapy for GD (407). The ATD will pass the placenta and treat the fetal hyperthyroidism, whereas the L-T4 is necessary to keep the mother euthyroid.

- **Recommendation 49**
  A combination regimen of levothyroxine and an antithyroid drug should not be used in pregnancy, except in the rare situation of isolated fetal hyperthyroidism. ***(Strong recommendation, High quality evidence)***

QUESTION 57 - WHAT ARE THE INDICATIONS AND TIMING FOR THYROIDECTOMY IN THE MANAGEMENT OF GRAVES' DISEASE DURING PREGNANCY?

Thyroidectomy should be considered in cases of allergies/contraindications to both ATDs; in the patient who is not compliant with drug therapy; and in women in whom euthyroidism cannot be achieved even on large doses of ATDs. If surgery is indicated, the second trimester is the optimal time. Thyroidectomy is often followed by a gradual, but not immediate, disappearance of TRAb, and withdrawal of ATD in the mother after thyroidectomy may lead to isolated fetal hyperthyroidism (403). High serum TRAb values before surgery indicate a risk for isolated fetal hyperthyroidism, and after maternal ATD withdrawal a program of careful fetal monitoring and possible therapy should be planned (403). In hyperthyroid patients not tolerating or non-responsive to antithyroid drug therapy, preparation for surgery with beta-blocking agents and a short course of potassium iodide solution (50-100 mg a day) are recommended (381). Potassium iodide preparation before surgery is also recommended in patients with other signs of active disease to reduce bleeding during surgery.

- **Recommendation 50**
  Thyroidectomy in pregnancy may be indicated for unique scenarios. If required, the optimal time for thyroidectomy is in the second trimester of pregnancy. If maternal TRAb concentration is high (> 3x upper reference for the assay) the fetus should be carefully monitored for development of fetal hyperthyroidism throughout pregnancy, even if the mother is euthyroid post-thyroidectomy**.** ***(Strong recommendation, High quality evidence)***

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QUESTION 58 - HOW SHOULD PREGNANT PATIENTS WITH GRAVES' DISEASE BE PREPARED FOR URGENT NON-THYROID SURGERY?

- **Recommendation 51**

  We concur with the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice consensus guidelines (written in 2011 and revised in 2015) (408) which state the following: "1) A pregnant woman should never be denied indicated surgery, regardless of trimester. 2) Elective surgery should be postponed until after delivery. 3) If possible, nonurgent surgery should be performed in the second trimester when preterm contractions and spontaneous abortion are least likely."
  In the setting of a patient with Graves' Disease undergoing urgent, non-thyroid surgery, if the patient is well controlled on ATD, no other preparation is needed. Beta-blockade should also be utilized if needed. (**Strong recommendation, Moderate quality evidence**)

QUESTION 59 - WHAT IS THE VALUE OF TRAb MEASUREMENT IN THE EVALUATION OF A PREGNANT WOMAN WITH GRAVES' HYPERTHYROIDISM?

Fetal risks in women with previous or current Graves' hyperthyroidism include: a) fetal hyperthyroidism, b) neonatal hyperthyroidism, c) fetal hypothyroidism, d) neonatal hypothyroidism, and e) central hypothyroidism. The above potential complications depend on several factors: 1) poor control of hyperthyroidism throughout pregnancy may induce transient central hypothyroidism (409,410); 2) excessive amounts of ATDs may be responsible for fetal and neonatal hypothyroidism, even if the mother is biochemically euthyroid (399,403) and 3) high levels of thyroid stimulating antibodies in the 2nd half of pregnancy may induce fetal and neonatal hyperthyroidism (411,412,413,414). TRAb is measurable in around 95% of patients with active Graves' hyperthyroidism and levels may remain high following ablation therapy, even more so after radioiodine treatment than surgical removal (415).

Indications for ordering a TRAb test in pregnant women with GD include: a) mothers with untreated or ATD-treated hyperthyroidism in pregnancy, b) a previous history of GD with past treatment with radioiodine or total thyroidectomy, c) a previous history of delivering an infant with hyperthyroidism, or d) a known history of thyroidectomy for the treatment of hyperthyroidism in pregnancy (416). In the majority of patients, maternal TRAb concentrations decrease with the progression of pregnancy, however, as in non-pregnant patients, the course of GD is variable.

The incidence of fetal and neonatal hyperthyroidism is between 1 and 5% in all women with active or a past history of Graves' hyperthyroidism, and is associated with increased fetal/neonatal morbidity and mortality if unrecognized and untreated (417). In a recent French study (418), follow-up of 47 newborns of mothers harboring measurable levels of TRAb in pregnancy showed that nine developed transient neonatal hyperthyroidism and five of these (9 % overall) had to be treated with ATD for a median duration of 60 days. A maternal TRAb serum concentration > 5 IU/L (approximately 3X the upper limit of normal for the assay) in the 2nd and 3rd trimester predicted neonatal hyperthyroidism with 100 % sensitivity and 43 % specificity. A similar TRAb level risk cut-off was found in a separate French study (419).

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A determination of serum TRAb in early pregnancy is helpful in detecting pregnancies at risk. A value > 5 IU/L or 3 times the upper limit of normal in a mother who previously received ablative therapy for Graves' disease is an indication for establishing close follow-up of the fetus in collaboration with a Maternal-Fetal-Medicine physician. Cases of overlooked isolated fetal hyperthyroidism leading to fetal loss in such women have repeatedly been published.

A determination of serum TRAb in late pregnancy in a mother who is still in need of ATD therapy to remain euthyroid, is helpful for detecting risk for neonatal hyperthyroidism. A value > 5 IU/L or 3 times the upper limit of normal in the mother indicates that the fetal thyroid may be strongly stimulated by TRAb passing through the placenta. After birth, any ATD from the mother is much more rapidly cleared in the neonate than are the TRAb, and the neonate may become hyperthyroid.

If TRAb becomes undetectable in a pregnant woman taking ATD, this is an indication that it may be feasible to reduce or withdraw the ATD, to protect the fetus against hypothyroidism and goiter.

In women who are in remission and euthyroid after a previous course of ATD therapy for Graves' disease, measurement of TRAb in pregnancy is not required (416).

- **Recommendation 52**
  a. If the patient has a past history of Graves' disease treated with ablation (radioiodine or surgery), a maternal serum determination of TRAb is recommended at initial thyroid function testing during early pregnancy. ***(Strong recommendation, Moderate quality evidence)***
  b. If maternal TRAb concentration is elevated in early pregnancy, repeat testing should occur at weeks 18-22. ***(Strong recommendation, Moderate quality evidence)***
  c. If maternal TRAb is undetectable or low in early pregnancy, no further TRAb testing is needed***. (Weak recommendation, Moderate quality evidence)***
  d. If a patient is taking ATDs for treatment of Graves' hyperthyroidism when pregnancy is confirmed, a maternal serum determination of TRAb is recommended. (***Weak recommendation, Moderate quality evidence)***
  e. If the patient requires treatment with ATDs for Graves' disease through mid pregnancy, a repeat determination of TRAb is again recommended at weeks 18-22. ***(Strong recommendation, Moderate quality evidence)***
  f. If elevated TRAb is detected at weeks 18-22 or the mother is taking ATD in the third trimester, a TRAb measurement should again be performed in late pregnancy (weeks 30-34) to evaluate the need for neonatal and postnatal monitoring. ***(Strong recommendation, High quality evidence)***

QUESTION 60 - UNDER WHAT CIRCUMSTANCES SHOULD ADDITIONAL FETAL ULTRASOUND MONITORING FOR GROWTH, HEART RATE, AND GOITER BE PERFORMED IN WOMEN WITH GRAVES' HYPERTHYROIDISM IN PREGNANCY?

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Serial ultrasound examinations may be performed for the assessment of gestational age, fetal viability, amniotic fluid volume, fetal anatomy, and detection of malformations. Fetal wellbeing may be compromised in the presence of elevated TRAb, uncontrolled hyperthyroidism, and pre-eclampsia (349,420,421,422). Signs of potential fetal hyperthyroidism that may be detected by ultrasonography include fetal tachycardia (heart rate >170 bpm, persistent for over 10 minutes), intrauterine growth restriction, presence of fetal goiter, (the earliest sonographic sign of fetal thyroid dysfunction), accelerated bone maturation, signs of congestive heart failure, and fetal hydrops (411,421,422,423). A team approach to the management of these patients is required, including an experienced obstetrician or maternal-fetal-medicine specialist, neonatologist, and anesthesiologist. In most cases, the diagnosis of fetal hyperthyroidism should be made on clinical grounds based on maternal history, interpretation of serum TRAb levels, and fetal ultrasonography (396,411,422,423).

- **Recommendation 53**
  Fetal surveillance should be performed in women who have uncontrolled hyperthyroidism in the second half of pregnancy, and in women with high TRAb levels detected at any time during pregnancy (greater than 3x the upper limit of normal). A consultation with an experienced obstetrician or maternal-fetal medicine specialist is recommended. Monitoring may include ultrasound to assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 61 - WHEN SHOULD UMBILICAL BLOOD SAMPLING BE CONSIDERED IN WOMEN WITH GRAVES' DISEASE IN PREGNANCY?

Umbilical cord blood sampling (cordocentesis) is associated with both fetal mortality and morbidity (424,425). It has been utilized when a mother is TRAb positive and treated with antithyroid drugs, a fetal goiter is present, and the thyroid status of the fetus is unclear (403,411,426). The presence of elevated TRAb antibodies alone is not an indication for cordocentesis (427).

- **Recommendation 54**
  Cordocentesis should be used in rare circumstances and performed in an appropriate setting. It may occasionally be of use when fetal goiter is detected in women taking antithyroid drugs to help determine whether the fetus is hyperthyroid or hypothyroid.
  (Weak recommendation, Low quality evidence)

Recently, biological assays able to distinguish between stimulating and blocking TSH-receptor antibodies have become commercially available (428). The use of such assays for characterization of TRAb biological activity may theoretically make cordocentesis unnecessary, though the complexity of differential clearance of stimulatory and blocking antibodies should be considered (see Section X – Fetal and Neonatal Considerations).

QUESTION 62 - HOW SHOULD HYPERTHYROIDISM CAUSED BY AUTONOMOUS THYROID NODULES BE HANDLED IN PREGNANCY

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One or more autonomous thyroid nodules is a common cause of hyperthyroidism in populations with current or previous mild to moderate iodine deficiency (429). However, even in such areas this type of hyperthyroidism is quite rare under the age of 40 years (430). Hyperthyroidism caused by autonomous nodules tends to develop more insidiously and be less severe than in GD.

In pregnancy, a major difference from GD is that no TRAb is produced by the mother, and consequently the fetal thyroid is not stimulated as it is in GD. Therefore, ATD therapy to make the mother euthyroid would significantly increase the risk of hypothyroidism and goiter in the fetus. Acknowledging limited data on this subject, if ATDs are required in this setting, careful monitoring of the fetus should occur. Furthermore, the dose of ATD should be kept low, and maternal surgical therapy with removal of autonomous nodule(s) considered if signs of fetal hypothyroidism develop. Generally, if possible, ablative therapy should be considered before conception for hyperthyroidism caused by thyroid autonomy in women seeking future pregnancy.

If only low-grade autonomous thyroid hormone production with subclinical hyperthyroidism is present in a non-pregnant woman, the physiological increase in thyroid hormone needs may ameliorate any hyperthyroidism in pregnancy. On the other hand, the early pregnancy high hCG level may theoretically activate non-affected normal thyroid tissue and increase thyroid secretion in early pregnancy. Furthermore, hormone production in autonomous thyroid nodules will depend on the available amount of iodine. Therefore, women with such disease should probably refrain from taking iodine-containing supplements in pregnancy.

- **Recommendation 55**
  If ATD therapy is given for hyperthyroidism caused by autonomous nodules, the fetus should be carefully monitored for goiter and signs of hypothyroidism during the 2nd half of pregnancy. A low dose of ATD should be administered with the goal of maternal FT4 or TT4 concentration at or moderately above the reference range. ***(Strong recommendation, Low quality evidence)***

QUESTION 63 - WHAT ARE THE ETIOLOGIES OF THYROTOXICOSIS IN THE POSTPARTUM PERIOD?

The most common cause of thyrotoxicosis in the postpartum period is postpartum thyroiditis (PPT), with a thyrotoxicosis prevalence of 4% (431,432) (see Section XII). Many cases are mild, of short duration, and spontaneously revert to euthyroidism. More severe cases in need of a short course of beta-blockers are seen in patients with high levels of TPO-antibodies, and they are often followed by a period of hypothyroidism. The majority of women return to euthyroidism by one year postpartum (433,434).

The postpartum increase in thyroid autoimmunity is also associated with a 3-4 fold increase in the incidence of new GD (401), in addition to the increase in the risk of relapse of GD in remission after previous ATD therapy. In one study, the overall relapse rate of Graves' disease following a pregnancy was 84%, as compared to a relapse rate of 56% in women who did not become pregnant (404).

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QUESTION 64 - HOW SHOULD GRAVES' HYPERTHYROIDISM BE TREATED IN LACTATING WOMEN?

See Section XI.

IX. Thyroid Nodules and Thyroid Cancer during Pregnancy

Thyroid nodules and thyroid cancer discovered during pregnancy present unique challenges to both the clinician and the mother. A careful balance is required between making a definitive diagnosis and instituting treatment while avoiding interventions that may adversely impact the mother, the health of the fetus, or the maintenance of the pregnancy.

QUESTION 65 - WHAT IS THE PREVALENCE OF THYROID NODULES DURING PREGNANCY?

Three studies have evaluated the prevalence of thyroid nodules during pregnancy, the impact of pregnancy on nodular size, and the proportion of women who have new nodules detected during pregnancy. All three studies were performed in areas with mild to moderate iodine deficiency (Brussels, China, and Germany), with the majority using ultrasound examination of the gland. The prevalence of thyroid nodules varied between 3% and 21% (187,435,436) and increased with increasing parity (9.4% without a prior pregnancy, 20.7% with one prior pregnancy, 20.7% with two prior pregnancies, and 33.9% with three or more prior pregnancies) (435). In the Belgian study, 60% of nodules doubled in size during pregnancy, yet remained between 5-12 mm (187). The maximum diameter of the dominant nodule did not increase during pregnancy in the Chinese study (mean diameter was 5.1 mm, 5.1 mm and 5.5 mm, in the first, second and third trimester respectively). However, an increase in nodular volume was reported during pregnancy, with a return to first trimester volumes by the third postpartum month (436). The studies in Belgium and Germany reported that 11 to 20 percent of women with a nodule detected in the first trimester of pregnancy developed a second nodule through the course of pregnancy (187,436). Increasing age is associated with an increase in the proportion of pregnant women who have thyroid nodules (187,436).

QUESTION 66 - WHAT IS THE PREVALENCE OF THYROID CANCER IN WOMEN WITH THYROID NODULES DISCOVERED DURING PREGNANCY?

Data regarding the prevalence of thyroid cancer derive from three retrospective studies performed at three tertiary referral centers (Mayo Clinic, George Washington University Hospital, and Mount Sinai Hospital-Toronto), one prospective study, and a retrospective study of the California Cancer Registry. The research performed at the referral centers revealed a 15% (6/40-Mayo Clinic (437), 12% (7/57-George Washington Hospital (438), and 43% (7/16 -Mount Sinai Hospital-Toronto (439) rate of thyroid malignancy. All three studies are limited by two

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major methodological flaws. The first, and most problematic, is selection bias. The population studies consisted of women referred for diagnosis and treatment at major referral centers. As such, they are not representative of the population of pregnant women with thyroid nodules detected during pregnancy. Instead, they represent a select group of women referred to a tertiary medical center due to physician concern for thyroid malignancy. Consequently, they likely represent an over-representation of the prevalence of thyroid malignancy during pregnancy. Secondly, each study was retrospective in nature and, therefore, neither the accuracy of the diagnosis nor the completeness of case identification within the database could be verified. The lone prospective study investigated the prevalence of thyroid cancer during pregnancy in 212 Chinese women. The study found a 15.3 % (34/221) rate of thyroid nodules and a 0% rate of malignancy. Interpreting these data is hampered by the limited number of women enrolled in the study (436). The final study consisted of a population-based retrospective analysis of all obstetrical deliveries in California between the years 1991 through 1999 identified by cross referencing maternal/neonatal hospital discharges in California and the California Cancer Registry (n=4,846,505 women). A prevalence of thyroid cancer in pregnancy of 14.4/100,000 was reported, with papillary cancer being the most frequent pathological type (440). Timing of diagnosis of the thyroid malignancy was as follows: 3.3/100,000 cases diagnosed before delivery, 0.3/100,000 at delivery, and 10.8/100,000 within one year postpartum.

QUESTION 67 - WHAT IS THE OPTIMAL DIAGNOSTIC STRATEGY FOR THYROID NODULES DETECTED DURING PREGNANCY?

History and physical examination

The patient with a thyroid nodule should be asked about a family history of benign or malignant thyroid disease, familial medullary thyroid carcinoma, multiple endocrine neoplasia type 2 (MEN 2), familial papillary thyroid carcinoma, and a familial history of a tumor syndrome predisposing to thyroid cancer syndrome (e.g., Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome [Cowden's disease], familial adenomatous polyposis, Carney complex, or Werner syndrome) (441,442,443). The malignancy risk is higher for nodules detected in both adult survivors of childhood cancers where treatment involved head/neck/cranial radiation and those exposed to ionizing radiation before 18 years of age (444,445). Thorough palpation of the thyroid and neck inspection for cervical nodes is essential (446).

Ultrasound

Thyroid ultrasound is the most accurate tool for detecting thyroid nodules, determining their sonographic features and pattern, monitoring growth, and evaluating cervical lymph nodes. The recent 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer should be referenced for diagnostic use and performance of thyroid and neck sonography as well as for decision-making regarding fine-needle aspiration (FNA) for thyroid nodules (443). Recent reports have validated that the identification of defined nodule sonographic patterns representing constellations of sonographic features is more robust for malignancy risk correlation than that associated with individual ultrasound characteristics (447,448). Hence, a high-suspicion sonographic pattern that includes solid hypoechoic nodules with irregular borders and microcalcifications correlates with a >70%

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chance of cancer compared to the very low suspicion pattern of a noncalcified mixed cystic solid or spongiform nodule (<3% cancer risk). The 2015 ATA guidelines (443, Recommendation 9) recommend different FNA size cut-offs based upon 5 defined sonographic patterns and their associated risk stratification for thyroid cancer (**Table 9**).

Thyroid function tests

All women with a thyroid nodule should have a TSH performed (449,450). Thyroid function tests are usually normal in women with thyroid cancer. In non-pregnant women, a subnormal serum TSH level may indicate a functioning nodule, which is then evaluated with scintigraphy because functioning nodules are so rarely malignant that cytologic evaluation is not indicated. However, pregnancy produces two hurdles for following this algorithm. First, the lower limit of the TSH reference range decreases, especially during early gestation, making it difficult to differentiate what is normal for pregnancy from potential nodular autonomous function. Second, scintigraphy with either technetium pertechnetate or ^{123}I is contraindicated in pregnancy (see below).

Calcitonin and thyroglobulin

As within the general population, the routine measurement of calcitonin remains controversial (451). Calcitonin measurement may be performed in pregnant women with a family history of medullary thyroid carcinoma or multiple endocrine neoplasia 2 or a known *RET* gene mutation. However, the utility of measuring calcitonin in all pregnant women with thyroid nodules has not been evaluated. The pentagastrin stimulation test is contraindicated in pregnancy (452).

In the presence of an *in situ* thyroid gland, serum thyroglobulin measurements are neither sensitive nor specific for thyroid cancer and can be elevated in many benign thyroid disorders (453). Thus, serum thyroglobulin measurement is not recommended.

Fine Needle Aspiration

Fine needle aspiration is a safe diagnostic tool in pregnancy and may be performed in any trimester (454,455,456,457,458,459,460,461,462,463). Two retrospective case series of FNAs performed during pregnancy, involving a total of 94 patients, have been published. In those cases where surgery was performed, pathological examination of the specimens confirmed the diagnosis of all FNAs classified by cytology as either benign or malignant. Six of the 16 (37.5%) cases reported by cytology as suspicious for malignancy were found to be malignant at pathological examination (437,438). Pregnancy does not appear to alter a cytological diagnosis of thyroid tissue obtained by FNA, but there have been no prospective studies to evaluate potential differences in FNA cytology obtained during pregnancy versus in the nonpregnant state. Since overall survival does not differ if surgery is performed during or after gestation in patients diagnosed with thyroid cancer during pregnancy (464,465,466), patient preference for timing of FNA (during pregnancy or postpartum) should be considered.

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Radionuclide scanning

^{131}I readily crosses the placenta and the fetal thyroid begins to accumulate iodine by 12-13 weeks gestation (467). There are reports of inadvertent administration of therapeutic ^{131}I therapy for treatment of hyperthyroidism during unsuspected pregnancy. If ^{131}I is given after 12-13 weeks gestation, it accumulates in the fetal thyroid resulting in fetal/neonatal hypothyroidism. In this scenario, The International Atomic Energy Agency (IAEA) recommends intervention with 60-130 mg of stable potassium iodide given to the mother only if the pregnancy is discovered within 12 hours of ^{131}I administration. This will partially block the fetal thyroid, hence reducing fetal thyroid ^{131}I uptake (468). However, if maternal treatment occurs prior to 12 weeks, the fetal thyroid does not appear to be damaged (469,470,471). Rather, the issue is the fetal whole body radiation dose due to gamma emissions from ^{131}I in the maternal bladder, which is in the range of 50-100 mGy/GBq of administered activity. This dose is decreased by hydrating the mother and by encouraging frequent voiding (468). No studies have specifically examined whether scanning doses of ^{123}I or technetium pertechnetate have adverse fetal effects if used during gestation. In general, these are contraindicated because all maternal radionuclides are associated with a fetal irradiation resulting from both placental transfer and external irradiation from maternal organs, specifically the bladder. Again, both maternal hydration and frequent voiding reduce fetal exposure (468).

The optimal diagnostic strategy for thyroid nodules detected during pregnancy is based on risk stratification. All women should have the following: a complete history and clinical examination, serum TSH measurement, and ultrasound of the neck.

- **Recommendation 56**
  For women with suppressed serum TSH levels that persist beyond 16 weeks gestation, FNA of a clinically relevant thyroid nodule may be deferred until after pregnancy. At that time, if serum TSH remains suppressed, a radionuclide scan to evaluate nodule function can be performed if not breastfeeding. ***(Strong recommendation, Low quality evidence)***

- **Recommendation 57**
  The utility of measuring calcitonin in pregnant women with thyroid nodules is unknown. The task force cannot recommend for or against routine measurement of serum calcitonin in pregnant women with thyroid nodules. ***(No recommendation, Insufficient evidence)***

- **Recommendation 58**
  Thyroid nodule FNA is generally recommended for newly detected nodules in pregnant women with a non-suppressed TSH. Determination of which nodules require FNA should be based upon the nodule's sonographic pattern as outlined in **Table 9**. The timing of FNA, whether during gestation or early postpartum, may be influenced by the clinical assessment of cancer risk, or by patient preference. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 59**
  Radionuclide scintigraphy or radioiodine uptake determination should not be performed during pregnancy. ***(Strong recommendation, High quality evidence)***

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QUESTION 68 - DOES PREGNANCY IMPACT THE PROGNOSIS OF NEWLY DIAGNOSED THYROID CARCINOMA?

Six studies have compared the diagnostic features and prognosis of women diagnosed with differentiated thyroid cancer (DTC) either during gestation or within the first year postpartum to nonpregnant women (464,465,466,472,473, 474). None of the studies were RCTs, all were retrospective, and the size of many of the studies was limited. Four studies either predate or do not use the contemporary tools for recurrence detection, including sensitive serum thyroglobulin (Tg) assays and neck sonography (464,465,466,473). Using large database evaluation (464,465,466), the analyzed outcomes were either overall survival or disease-free survival, neither of which differed between the two groups. This is not unexpected, as the vast majority (>99%) of both the pregnant and nonpregnant populations had stage 1 disease. In addition, all studies consistently found that timing of surgery, either during pregnancy or deferred until postpartum, did not affect survival.

Recently, using both sonography and sensitive Tg assays, two studies from referral centers in Italy have reported higher persistence or recurrence rates in women diagnosed with thyroid cancer during pregnancy or within 12-24 months of delivery compared to both nulliparous women and those diagnosed after a longer interval postpartum (472,474). DTC persistence or recurrence was defined as 1) either stimulated or suppressed serum Tg >2 ng/ml, 2) increasing levels of Tg autoantibodies, 3) sonography detection of metastatic lymph nodes, or 4) uptake outside the thyroid bed on scintigraphy. Subjects were followed for a median of about 6 years after definitive therapy. Vannuchi et al. observed a much higher than expected persistence/recurrence rate (60%) in the pregnant/early postpartum group than otherwise anticipated for Stage 1 disease, compared to 4% in women diagnosed more than 12 months after delivery and 13% in nulliparous women. The majority of the recurrences (67%) were identified by Tg or TgAb criteria without identification of structural disease, so it is unclear if Tg/TgAb detection is associated with other confounding factors such as potentially less aggressive surgery if done during gestation. Messuti et al. reported a more typical-for-early-stage disease recurrence rate of 10%, but this was statistically higher than the 1.3% for women diagnosed 2 years after delivery and 4.3% for nulliparous women. No details for recurrence classification, biochemical versus structural, were provided. Importantly, delaying surgery until after delivery did not further affect recurrence rates among women diagnosed with DTC during gestation in either study. Although there are several potential explanations for the poorer prognosis of pregnant/early postpartum women versus the comparator groups, these are not consistent findings in the two studies. Metastatic cervical adenopathy at diagnosis was more frequent in pregnant/postpartum women compared to the other groups in one study (63% vs. ~40%) (472) but not in the other (474). Vannucchi et al. documented more frequent presence of estrogen receptor (ER) α in the tumors of women diagnosed during pregnancy/early postpartum as compared to the other two groups, which may indicate that the poorer prognosis is related to estrogen-mediated growth and stimulation of the MAPK pathway. However, this was not confirmed in the study by Messuti et al. (474). The discrepancy may be due to methodologic issues, because a less-dilute ER antibody was employed in the study with the positive findings. Hence, there is a recent observation of higher persistence/recurrence rates for women diagnosed

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with DTC during or immediately after pregnancy, without elucidation of pathophysiologic mechanisms. Further studies may help to clarify causality. Importantly, survival is not compromised.

The impact of pregnancy on women with medullary or anaplastic carcinoma is unknown.

QUESTION 69 - WHAT ARE THE PERI-OPERATIVE RISKS TO MOTHER AND FETUS OF THYROID SURGERY DURING PREGNANCY?

Surgery is the treatment of choice for differentiated thyroid carcinoma. As deferring surgery until postpartum has not been associated with a worse prognosis, it is imperative to assess maternal and neonatal complications before recommending an operation during pregnancy. Between 1986 and 2008, nine studies evaluated the impact of thyroidectomy during pregnancy on a total of 113 patients (study size ranged from 1 to 96) (437,441,442,444,446,475,476,477,478). The majority, but not all, of the operations were performed in the second trimester. There were no maternal or fetal complications in any of the studies. A 2009 population-based study of non-federal hospitals in the United States compared 201 pregnant women who underwent thyroid and parathyroid surgery during pregnancy with 31,155 similarly treated non-pregnant women. One hundred sixty-five operations were thyroid-related and 46% of the women had thyroid cancer. Pregnant patients had a higher rate of endocrine and general complications, longer lengths of stay, and higher hospital costs. The fetal and maternal complication rates were 5.5% and 4.5%, respectively (479). Interpretation of the results of this study is difficult as there were substantial baseline differences between the two groups. Pregnant women were more likely to have either urgent or emergent admissions and had a higher percentage of government insurance. However, surgical volume was also an independent predictor of poor outcomes, so that if surgery is performed during pregnancy, an experienced surgeon is preferred. Recently, a study from Japan focused on 45 patients with differentiated thyroid cancer, of whom 24 had thyroidectomy during pregnancy (19 during the second trimester) and 21 had surgery after delivery. The groups were compared with regard to disease and other factors. There was no difference in recurrence rates in the mothers and there were no pregnancy losses or birth defects. The authors concluded that although thyroidectomy can be performed safely in the second trimester, surgery after delivery is recommended for most patients with non-aggressive differentiated thyroid cancer (480). Thus, in instances where surgery during pregnancy is indicated or desired, it should be performed in the second trimester in order to minimize complications to both the mother and fetus (altered organogenesis and spontaneous abortion in the first trimester; pre-term labor and delivery in the third trimester) (481), preferably by an experienced thyroid surgeon. The risk of post-thyroidectomy maternal hypothyroidism and hypoparathyroidism should also be considered.

QUESTION 70 - HOW SHOULD CYTOLOGICALLY BENIGN THYROID NODULES BE MANAGED DURING PREGNANCY?

Although pregnancy is a risk factor for modest progression of nodular thyroid disease, there is no evidence demonstrating that levothyroxine is effective in decreasing the size or

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arresting the growth of thyroid nodules during pregnancy. Hence, levothyroxine suppressive therapy for thyroid nodules is not recommended during pregnancy. Nodules that were benign on FNA but show rapid growth or US changes suspicious for malignancy should be evaluated with a repeat FNA and be considered for surgical intervention. In the absence of rapid growth, nodules with biopsies which are either benign do not require surgery during pregnancy (482).

- **Recommendation 60**
  Pregnant women with cytologically benign thyroid nodules do not require special surveillance strategies during pregnancy, and should be managed according to the 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 71 - HOW SHOULD CYTOLOGICALLY INTDETERMINATE NODULES BE MANAGED DURING PREGNANCY?

There have been no prospective studies evaluating the outcome and prognosis of women with an FNA that is interpreted as either atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), or suspicious for malignancy (SUSP). The reported malignancy rates associated with these cytologic diagnoses range from 6-48% for AUS/FLUS, 14-34% for SFN and 53-87% for SUSP (483). Although molecular testing for cytologically indeterminate nodules is now being considered, no validation studies address application of these tests in pregnant women. It is theoretically possible that thyroid gestational stimulation may alter a nodule's gene expression and change diagnostic performance of molecular tests based upon RNA expression, whereas testing based upon either single base pair DNA mutations or translocations would be less likely to be affected.

Since prognosis for differentiated thyroid cancer diagnosed during pregnancy is not adversely impacted by performing surgery postpartum, it is reasonable to defer surgery until following delivery. As the majority of these women will have benign nodules, levothyroxine therapy during pregnancy is not recommended.

- **Recommendation 61**
  Pregnant women with cytologically indeterminate (AUS/FLUS, SFN, or SUSP) nodules, in the absence of cytologically malignant lymph nodes or other signs of metastatic disease, do not routinely require surgery while pregnant. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 62**
  During pregnancy**,** if there is clinical suspicion of an aggressive behavior in cytologically indeterminate nodules, surgery may be considered. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 63**
  Molecular testing is not recommended for evaluation of cytologically indeterminate nodules during pregnancy. ***(Strong recommendation, Low quality evidence)***

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QUESTION 72 - HOW SHOULD NEWLY DIAGNOSED THYROID CARCINOMA BE MANAGED DURING PREGNANCY?

The 2015 ATA guidelines (443) recommend that a nodule with cytology indicating papillary thyroid carcinoma discovered early in pregnancy should be monitored sonographically and, if either it grows substantially by 24 weeks gestation (50% in volume and 20% in diameter in two dimensions), or if metastatic cervical lymph nodes are present, surgery should be considered in the second trimester. However, if it remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be performed after delivery. Surgery in the second trimester is an option if the differentiated thyroid cancer is advanced stage at diagnosis or if the cytology indicates medullary or anaplastic carcinoma.

If surgery is not performed, the utility of thyroid hormone therapy targeted to lower serum TSH levels to improve the prognosis of differentiated thyroid cancer diagnosed during gestation is not known. Because higher serum TSH levels may be correlated with a more advanced stage of cancer at surgery (484), if the patient's serum TSH is >2 mU/L, it may be reasonable to initiate thyroid hormone therapy to maintain the TSH between 0.3 to 2.0 mU/L for the remainder of gestation.

- **Recommendation 64**
  PTC detected in early pregnancy should be monitored sonographically. If it grows substantially before 24-26 weeks gestation, or if cytologically malignant cervical lymph nodes are present, surgery should be considered during pregnancy. However, if the disease remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 65**
  The impact of pregnancy on women with newly diagnosed medullary carcinoma or anaplastic cancer is unknown. However, a delay in treatment is likely to adversely impact outcome. Therefore, surgery should be strongly considered, following assessment of all clinical factors. ***(Strong recommendation, Low quality evidence)***

QUESTION 73 - WHAT ARE THE TSH GOALS FOR PREGNANT WOMEN WITH PREVIOUSLY TREATED THYROID CANCER RECEIVING LEVOTHYROXINE THERAPY?

Based on studies which have demonstrated a lack of maternal or neonatal complications from subclinical hyperthyroidism, it is reasonable to assume that the pre-conception degree of TSH suppression can be safely maintained throughout pregnancy. The appropriate level of TSH suppression depends upon pre-conception risk of residual or recurrent disease. According to the 2009 and 2015 ATA management guidelines for DTC (443,482), and the European Thyroid Association (ETA) consensus (485), the serum TSH should be maintained indefinitely below 0.1 mU/L in patients with persistent structural disease. Target TSH values are first based upon initial

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risk of recurrence determined post-operatively (2015 ATA guidelines Table 12) and then are modified based upon classification of the patient's response to therapy as defined in **Table 13** of the 2015 ATA guidelines. Hence, for a patient at initial high risk for recurrence, TSH suppression at or below 0.1 mU/L is recommended. If the patient then demonstrates an excellent response to therapy at one year with an undetectable suppressed serum Tg and negative imaging, the TSH target may rise to the lower half of the reference range.

The main challenge in caring for women with previously treated DTC is maintaining the TSH level within the pre-conception range. In a recent report (325), thyroid cancer patients were reported to require smaller LT4 dose increases than patients who had undergone thyroid ablation for benign thyroid disorders or patients with primary hypothyroidism. However, this was because the nonpregnant serum level TSH was <0.1 mU/L in 83% of the thyroid cancer prior to pregnancy and this target was not achieved during gestation. It is likely that if the pre-pregnancy TSH target level is maintained throughout gestation, the levothyroxine dosage increase will be similar to the ~49% required in ablated hypothyroidism. Patients require careful monitoring of thyroid function tests in order to avoid hypothyroidism.

Thyroid function should be evaluated as soon as pregnancy is confirmed. The adequacy of LT4 treatment should be checked four weeks after any LT4 dose change. The same laboratory should be utilized to monitor TSH and thyroglobulin levels before, during, and after pregnancy.

- **Recommendation 66**
  Pregnant women with thyroid cancer should be managed at the same TSH goal as determined pre-conception. TSH should be monitored approximately every 4 weeks until 16-20 weeks of gestation, and at least once between 26-32 weeks of gestation. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 74 - WHAT IS THE EFFECT OF THERAPEUTIC RADIOACTIVE IODINE TREATMENT ON SUBSEQUENT PREGNANCIES?

Following surgery for DTC, many patients will receive an ablative dose of radioactive iodine. The possible deleterious effect of radiation on gonadal function and the outcome of subsequent pregnancies has been evaluated by Sawka et al. and Garsi et al. (the latter collected 2673 pregnancies, 483 of which occurred after RAI treatment) (486,487). Neither study found an increased risk of infertility, pregnancy loss, stillbirths, neonatal mortality, congenital malformations, pre-term births, low birth weight, or death during the first year of life, or cancers in offspring.

Radioiodine (RAI) treatment may lead to suboptimal thyroid hormonal control during the month following administration. The potential adverse impact of this upon the pregnancy is described in Section VII. It therefore seems reasonable to wait a minimum of 6 months to ensure that thyroid hormonal control is stable before conceiving following RAI ablative therapy.

^{131}I may affect spermatogenesis. In one study following men after ^{131}I therapy, there was a dose-dependent increase in FSH levels and a reduction in normokinetic sperm (488).

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Therefore, it seems prudent for a man who has received ^{131}I to wait 120 days (the lifespan of sperm) after ^{131}I therapy before attempting to conceive.

- **Recommendation 67**
  Pregnancy should be deferred for 6 months after a woman has received therapeutic radioactive iodine (^{131}I) treatment. ***(Strong recommendation, Low quality evidence)***

QUESTION 75 - WHAT IS THE EFFECT OF TYROSINE KINASE INHIBITORS ON PREGNANCY?

Several tyrosine kinase inhibitor medications are now FDA-approved for the therapy of metastatic differentiated and medullary thyroid cancer. These include sorafenib, lenvatinib, and cabozantinib. All three drugs have demonstrated both teratogenicity and embryo toxicity in animals when administered at doses below the recommended human dose (489). There are no human studies. The FDA recommends that women be advised of the TKI potential risk to the fetus. However, specific advisories vary by medication. Furthermore, the use of any TKI must be guided by an assessment of risks to benefits that is also impacted by the stage of disease and recommended drug indications. For sorafenib, the FDA prescribing information counsels to avoid pregnancy while taking the drug. For lenvatinib, contraception is explicitly recommended. For cabozantinib, no additional warnings are listed (489).

QUESTION 76 - DOES PREGNANCY INCREASE THE RISK OF DTC RECURRENCE?

Five studies have evaluated the impact of pregnancy after a woman has been treated for DTC. Two were published five decades ago, predating contemporary tools for thyroid cancer surveillance (490,491). Still, Rosvoll et al. (490) demonstrated pregnancy did not accelerate tumor growth in the 22 women who had stable or slowly progressive metastatic disease. Hill et al. (491) found no difference in clinically detected thyroid cancer recurrence rates in 70 women who had one or more pregnancies following initial diagnosis of DTC and 109 women who had no subsequent pregnancies. A more recent study from Memorial Sloan Kettering reported on 36 women who became pregnant between 1997 and 2006, a median of 4.3 years after initial treatment for DTC (492). Although all had serum Tg testing, only 16 (44%) had ultrasound imaging before and after delivery. Disease progression occurred in one of the two women who had metastatic cervical lymph nodes on baseline imaging (the lymph node grew from 2.3 cm to 2.7 cm). The mean suppressed Tg after delivery was not significantly different than the pre-partum value. However, eight women had postpartum Tg values more than 20% higher than before pregnancy (three with known disease, five with no clinical evidence of disease). No evidence of recurrence was detected in the early postpartum period in women with negative pre-pregnancy neck US and a suppressed serum Tg <1 ng/ml. Two more recent studies (493,494) routinely used neck sonography and sensitive Tg assays to evaluate cancer progression during pregnancy. No recurrence was observed in 64 Brazilian women (48 papillary cancer and 16 follicular cancer) who had suppressed Tg levels <2 ng/ml and negative neck sonography pre-pregnancy. However, follow up was limited to only 6 months after delivery (493). Using a definition of disease-free as a suppressed Tg <0.9 ng/ml and negative neck US, Hirsch and colleagues followed 63 women who had given birth after receiving treatment for DTC (all

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papillary thyroid cancer) for a mean of 4.8 years. None of the 50 women categorized as disease-free had progression of disease. However, six of the 13 women (46%) with persistent disease pre-pregnancy experienced progression. Metastatic cervical lymph nodes grew in 50% of those with known pre-pregnancy nodal disease and new nodal metastases appeared in 2/7 with negative baseline sonography (494).

Thus, pregnancy does not pose a risk for tumor recurrence in women without structural or biochemical disease present prior to the pregnancy. Therefore, women with an excellent response to therapy as defined by the 2015 ATA guidelines (443) do not require additional monitoring during gestation. However, pregnancy may represent a stimulus to thyroid cancer growth in patients with known structural (ATA 2015 structural incomplete response to therapy) or biochemical (ATA 2015 biochemical incomplete response to therapy) disease present at the time of conception, and requires monitoring.

QUESTION 77 - WHAT TYPE OF MONITORING SHOULD BE PERFORMED DURING PREGNANCY IN A PATIENT WHO HAS ALREADY BEEN TREATED FOR DTC PRIOR TO PREGNANCY?

- **Recommendation 68**
  Ultrasound and thyroglobulin monitoring during pregnancy is not required in women with a history of previously treated differentiated thyroid carcinoma with undetectable serum thyroglobulin levels (in the absence of Tg autoantibodies) classified as having no biochemical or structural evidence of disease prior to pregnancy. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 69**
  Ultrasound and thyroglobulin monitoring should be performed during pregnancy in women diagnosed with well-differentiated thyroid cancer and a biochemically or structurally incomplete response to therapy, or in patients known to have active recurrent or residual disease. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 78 - WHAT TYPE OF MONITORING SHOULD BE PERFORMED DURING PREGNANCY IN A PATIENT WHO IS UNDER ACTIVE SURVEILLANCE FOR PAPILLARY THYROID MICROCARCINOMA?

Although FNA of sub-centimeter nodules in the absence of suspicious cervical adenopathy is not recommended by the 2015 ATA guidelines (443), there are times when this has been performed with subsequent diagnosis of a papillary thyroid microcarcinoma (PTMC). In some situations, women with this diagnosis may have chosen active surveillance. Observation with active surveillance has been demonstrated to be a viable option for patients cytologically diagnosed with PTMC (size <1cm) in the absence of suspicious lymph nodes or extrathyroidal invasion by sonographic imaging (495). Although tumor growth >3 mm and appearance of novel metastatic lymph nodes occurred respectively overall in 8% and 3.8% of a cohort of 1235 Japanese patients, progression was more likely in patients younger than 40 years of age. Therefore, the same group published their observations of 9 women with PTMC who became pregnant during active surveillance and compared outcomes to 27 age-matched nonpregnant

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women. During pregnancy, growth ≥3 mm occurred more frequently in pregnant (44%) than nonpregnant (11%) women (p=0.0497). There was no correlation between growth and gestational TSH or thyroglobulin levels, and novel metastatic cervical lymph nodes were not observed. Three of the four patients who experienced tumor growth had surgery postpartum, but the tumor decreased in size postpartum in the fourth patient who is still under active surveillance. Furthermore, the PTMC enlarged by less than 3 mm in the other five pregnant women, but then decreased in three postpartum (496). This supports the hypothesis that pregnancy is either permissive for or promotes growth of papillary thyroid cancer. While this may have no impact on overall health, it seems reasonable to monitor such women with serial sonographic evaluations.

- **Recommendation 70**
  Ultrasound monitoring of the maternal thyroid should be performed each trimester during pregnancy in women diagnosed with PTMC who are under active surveillance. ***(Weak recommendation, Low quality evidence)***

QUESTION 79 - WHAT SPECIAL CONSIDERATIONS SHOULD BE FOLLOWED FOR WOMEN WITH MEDULLARY CANCER DUE TO GERMLINE RET MUTATIONS?

Hereditary medullary thyroid cancer (MTC) may occur as a result of activating germline mutations of the *RET* oncogene. Over 100 mutations, duplications, insertions, or deletions involving RET have been identified in patients with hereditary MEN2a (including familial MTC) or MEN2b syndromes. The newly Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma have graded the most common mutations according to risk of aggressive MTC and likelihood of concomitant pheochromocytoma and hyperparathyroidism (497). For a woman with a given RET mutation with or without clinical MTC, who is either pregnant or contemplating conception, the associated risks of MTC aggressiveness combined with her own history may inform her about whether to seek genetic counseling. Both prenatal and pre-implantation genetic testing are available and the reader is referred to the excellent discussion in the 2015 ATA guidelines that culminates in Recommendation 12, "The duty to warn of genetic risk extends to both preconception and prenatal contexts. Genetic counseling about the options of pre-implantation or prenatal diagnostic testing should be considered for all RET mutation carriers of childbearing age, particularly those with MEN2B. Parents who do not wish to have prenatal *RET* gene mutation testing should be offered genetic counseling and informed of the availability of genetic testing of their child to detect a mutated *RET* allele. This is particularly important for mutations associated with the onset of MTC before 5 years of age." In addition, testing to exclude a pheochromocytoma should be done prior to pregnancy for all women with MEN2. No studies address the effect of pregnancy on MTC progression in patients with biochemical or structural evidence of residual or metastatic disease.

X. Fetal and Neonatal Considerations

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QUESTION 80 - WHAT IS THE RELATIONSHIP BETWEEN MATERNAL AND FETAL THYROID HORMONE STATUS?

Under normal circumstances the fetal hypothalamic-pituitary-thyroid system develops relatively independent of maternal influence because of the presence of the placenta, which regulates the passage of many substances, including T4, to the fetus. Circulating fetal thyroid hormone levels therefore largely reflect the stage of fetal maturation.

Thyroid hormone receptors are present in the fetal brain at low concentrations up to week 10 of gestation. Thyroid hormone receptor concentrations then rapidly increase 10-fold through week 16 of pregnancy (498).

Serum total T4 and free T4 are first measurable in low levels in fetal serum at 12-14 weeks of development (499,500,501). Based on values obtained by fetal cord sampling in normal pregnant women, it has been estimated that the mean fetal serum total T4 is 2 mcg/dL (26 nmol/L) at 12 weeks, and a relatively larger proportion is in the free form. Beginning in mid-gestation, the fetal total T4 concentration begins to increase and typically reaches values comparable to non-pregnant females (10 mcg/dL (138 nmol/L)) by 36 weeks. This rise in total T4 follows an increase in the serum TBG concentration due primarily to the stimulatory effects of maternal estrogen on the fetal liver. In addition, due to upregulation of the TSH receptor there is an increase in the fetal free T4 concentration from a mean of approximately 0.1 ng/dL (1.3 pmol/L) to 2 ng/dL (25.7 pmol/L), beginning early in the third trimester (502).

In contrast to T4, the fetal circulating levels of its active metabolite T3 remain significantly lower in fetal life than postnatally, whereas the inactive metabolites reverse T3 (rT3) and T3 sulfate are elevated. The fetal serum T3 concentration is approximately 6 ng/dL (0.09 nmol/L) at 12 weeks, rising to 45 ng/dL (0.68 nmol/L) at 36 weeks. Despite the low levels of circulating T3, brain T3 levels are 60-80% those of the adult by fetal age 20-26 weeks (503). This reflects the importance of local conversion of T4 to T3 in the brain itself. During the second trimester expression of type 2 deiodinase, which converts T4 to T3, increases in the fetal cerebral cortex in parallel to the T3 concentrations (504). T3 sulfate may also serve as an alternate source of T3 for the pituitary (505).

The serum concentration of TSH rises modestly from ~ 4 mU/L at 12 weeks to 8 mU/L at term, and is always higher than the corresponding maternal levels (500,506). The reason for this is not completely understood but may be a consequence of incomplete maturation of the hypothalamic-pituitary-thyroid axis and/or the high TRH levels in the fetus.

QUESTION 81 - WHAT IS THE ROLE OF PLACENTAL TRANSFER?

Thyroid Hormone

The placenta plays a key role in regulating the exchange of products between the mother and fetus. The amount of placental transfer and the consequent effect on fetal thyroid function varies widely.

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Under normal circumstances, the human placenta has modest permeability for T4 due to the predominance of placental deiodinase (D3), which serves to inactivate most of the thyroid hormone presented from the maternal to the fetal circulation. The iodide released by this process can be used as a substrate for fetal thyroid hormone synthesis. The placenta also expresses some D2 (an activating deiodinase), but placental D3 activity is approximately 200-fold greater than D2; the activity of both D2 and D3 falls as pregnancy progresses. The placenta also expresses a range of thyroid hormone transporters, binding proteins, sulfotransferases and sulfatases. The balance of all of these enzymatic processes determines the amount of T4 transfer that occurs (507).

In the first half of pregnancy, before fetal thyroid maturation, T4 is detectable in the fetal brain, indicating that mechanisms exist for small but significant transfer of maternal T4 to the fetal circulation (503,507). This transfer of maternal thyroid hormone is particularly important when the fetus is hypothyroid, and probably explains the normal or near-normal cognitive outcomes of babies diagnosed with severe congenital hypothyroidism at birth and treated adequately and sufficiently early following birth. For example, even in infants with congenital absence of thyroid peroxidase, the cord serum concentration of T4 is between 25 and 50% of normal (508). This maternal T4 disappears rapidly from the newborn circulation, with a half-life of approximately 3 to 4 days.

Iodine

Iodine is actively transported across the placenta from the maternal circulation to the fetus. The placenta actively concentrates iodine through expression of the sodium iodide transporter (NIS), the concentration of which increases with gestational age (509).

Immunoglobulin G (IgG)

Maternal autoantibodies of the IgG class are transported across the placenta from approximately midgestation onward by a cellular receptor termed the neonatal Fc receptor, thereby providing the fetus and neonate with humoral immune protection until the infant starts producing its own IgG (510). In mothers with autoimmune thyroid disease, autoantibodies to thyroid peroxidase (TPO), Tg, and the TSH receptor can be transmitted to the fetus in a similar fashion. Whereas TPOAbs and TGAbs do not significantly affect fetal or neonatal thyroid function, antibodies to the TSH receptor can stimulate or block thyroid hormonogenesis or be biologically neutral (511) (see sections VII and VIII on Hypothyroidism and Thyrotoxicosis). Maternal transmission of antibodies to thyroid hormone has also been reported as a cause of congenital hypothyroidism (512).

Hyperthyroidism generally develops only in babies born to mothers with the most potent (or highest concentrations of) stimulatory TRAb activity (513,514). This corresponds to 1-2% of mothers with Graves' disease, or 1 in 50,000 newborns, an incidence that is approximately four times higher than that for transient neonatal hypothyroidism due to maternal TSH receptor blocking antibodies (515). Some mothers have mixtures of stimulating and blocking antibodies in their circulation, the relative proportion of which may change over time. Not surprisingly, the

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clinical picture in the fetus and neonate of these mothers is complex and depends not only on the relative proportion of each activity in the maternal circulation at any one time but on the rate of their clearance from the neonatal circulation postpartum. Thus, one affected mother gave birth, in turn, to a normal infant, a baby with transient hyperthyroidism, and one with transient hypothyroidism (516). In another neonate, the onset of hyperthyroidism did not become apparent until 1-2 months postpartum when the higher-affinity blocking antibodies had been cleared from the neonatal circulation (517). In the latter case, multiple TSH receptor stimulating and blocking antibodies were isolated from maternal peripheral lymphocytes. Each monoclonal antibody recognized different antigenic determinants ("epitopes") on the receptor and had different functional properties (518). Occasionally, neonatal hyperthyroidism may occur in infants born to hypothyroid mothers. In these situations, the maternal thyroid has been destroyed by prior radioablation or surgery so that potent thyroid stimulating antibodies, present in the maternal circulation, affect the fetal thyroid, but not the maternal thyroid.

TSH receptor blocking, Ab-induced congenital hypothyroidism, is much less common than neonatal Graves' disease but should be suspected in any child with congenital hypothyroidism born to a mother with severe autoimmune thyroid disease, especially if there is a history of a similarly affected sibling (515). Blocking Ab-induced congenital hypothyroidism is important to identify because it identifies a child who is likely to have transient disease (515,519). Affected infants may have significantly impaired cognitive outcomes despite early and adequate postnatal treatment if maternal hypothyroidism was present and untreated during gestation (520). The half-life of IgG is 1 to 2 weeks, and the duration of the antibody-induced hypothyroidism is usually about 3 months, but may be longer.

Significant transplacental transfer of maternal TRH occurs, but not maternal TSH, hCG or Tg. Importantly, both antithyroid drugs (PTU and MMI) as well as TSH receptor Abs can pass from the mother and the fetus. This may have significant effects on fetal and neonatal thyroid function, as discussed elsewhere.

QUESTION 82 - WHEN MATERNAL THYROID ABNORMALITIES ARE DETECTED, HOW AND WHEN SHOULD INFORMATION BE PROVIDED TO THE NEONATOLOGIST OR PEDIATRICIAN?

QUESTION 83 -WHAT INFORMATION SHOULD BE PROVIDED TO THE NEONATOLOGIST OR PEDIATRICIAN?

Most infants born to women with known thyroid illness are healthy. Furthermore, all newborn infants in the United States are screened for thyroid dysfunction as part of universal screening mandates. Nonetheless, maternal thyroid illness, abnormal maternal thyroid function, the presence of maternal TSH receptor Abs, and/or the use of antithyroid medications during gestation can each contribute to adverse effects in the newborn. Therefore, knowledge of these facts is important and should be documented in the newborn infant's medical record. In many cases, direct communication with the neonatologist or pediatrician is recommended, especially in the setting of severe maternal hyperthyroidism or maternal use of antithyroid drugs at any time throughout pregnancy. The etiology, timing, severity, and treatment of maternal thyroid disease should all be conveyed. In women with Graves' disease (even if previously ablated with ^{131}I or

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athyreotic following surgery) concentrations of circulating TRAb should be assessed at initial thyroid function testing in early pregnancy, and if TRAb is positive, again at weeks 18-22 (see Section VIII). Such information should be documented and conveyed to the pediatrician, since maternally-derived thyroid antibodies as well as antithyroid medication, can transfer to the fetus and affect newborn thyroid health.

- **Recommendation 71**
  A history of maternal thyroid illness, use of antithyroid medications (PTU, MMI) during gestation, or measurements of abnormal maternal thyroid function or TRAb during gestation should be communicated to the newborn's neonatologist or pediatrician. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 72**
  The severity of maternal and fetal thyroid illness should guide the timing of communication. Severe, progressive, or complex thyroid illness during pregnancy mandates communication with the neonatologist or pediatrician before birth and consideration of consultation with a pediatric endocrinologist. Most other illness is optimally communicated shortly after birth. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 84- SHOULD ALL NEONATES BE SCREENED FOR THYROID DYSFUNCTION?

Congenital hypothyroidism is one of the most frequent treatable causes of intellectual impairment, and newborn screening for the detection of congenital hypothyroidism is performed routinely in all 50 states of the United States, as well as in Canada, Europe, Israel, Japan, Australia and New Zealand (521). Screening programs are also being introduced in many developing countries, accounting overall for approximately one-third of the world's population (521). Blood spot specimens eluted from filter paper are utilized. The optimal timing of measurement is at 2-5 days of age, in order to avoid confounding by the physiologic surge in neonatal TSH, which occurs shortly after birth. Some programs employ primary T4 screening with TSH measurement when specimens demonstrate a value below a specified cut-off. Others use a primary TSH determination with reflex T4 strategy. The introduction of newborn screening for congenital hypothyroidism has led to the virtual elimination of intellectual impairment due to hypothyroidism so long as early and adequate postnatal levothyroxine treatment is initiated immediately (522,523).

- **Recommendation 73**
  All newborns should be screened for hypothyroidism by blood spot analysis typically 2-4 days after birth. ***(Strong recommendation, High quality evidence)***

QUESTION 85 -HOW IS NEONATAL HYPOTHYROIDISM TREATED?

In women receiving antithyroid drugs at the time of delivery, transplacental transfer of the medication can potentially induce neonatal hypothyroidism. In such cases, neonatal metabolism removes the remaining MMI or PTU from the newborn circulation. This results in the return of normal thyroid function, typically within 3 to 5 days. For neonates with congenital

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hypothyroidism, levothyroxine must be administered. The recommended starting dose for full-term infants is 10 to 15 mcg/kg/day, and depends on the severity of the initial hypothyroidism (522,523). In premature hypothyroid infants a lower dose is generally utilized. For optimal cognitive outcomes, therapy should be initiated within two weeks of life. Both inadequate and excess thyroid hormone replacement may be harmful, so close follow up is important, particularly during the first three years of life. During this time, brain development is thyroid hormone-dependent. Age-dependent normative values for TSH and T4 should be used to guide therapy. Until further information becomes available, infants with severe congenital hypothyroidism (i.e. - initial serum TSH concentration >100 mU/L) should remain on a single formulation of L-thyroxine without substitution (524). Treatment should be guided by a pediatric endocrinologist or experienced pediatrician.

The presence of a goiter in a newborn should prompt referral to a pediatric endocrinologist. An ultrasound examination should be performed to evaluate the patency of the trachea. A goiter may reflect a hypothyroid or hyperthyroid state in response to maternal thyroid illness, or overtreatment with antithyroid medications. Regardless, close observation and urgent treatment may be required to achieve a euthyroid state and avoid airway compromise in the newborn.

For a more detailed discussion of this and other aspects of neonatal hypothyroidism, the reader is referred to several recent excellent reviews and guidelines (522,523,525).

QUESTION 86 - HOW IS NEONATAL HYPERTHYROIDISM TREATED?

Most neonatal hyperthyroidism is caused by maternal transfer of TRAb to the fetus. Typically, neonatal Graves' disease does not present until the end of the first week of life when maternal antithyroid drug, but not the TRAb, have been cleared from the neonatal circulation. This may be delayed in babies born to mothers with a mixture of stimulating and blocking antibodies. Thus, results on newborn screening may be paradoxically normal. A high degree of suspicion for infants at risk is important.

The conventional treatment for neonatal hyperthyroidism is PTU 5 to10 mg/kg administered in divided doses. However recent evidence of rare hepatotoxicity due to this agent has led to a switch to MMI therapy (0.5 to 1 mg/day) by many pediatric endocrinologists. Propranolol (2 mg/kg) may be added if the hyperthyroidism is severe. Close follow up of the affected newborn is important, with downward adjustment in the dose of antithyroid drug required as the hyperthyroidism resolves. The usual duration of neonatal Graves' disease is 1 - 3 months, but depends on antibody potency. Separate from neonatal Graves' disease (which is self-limited), neonatal hyperthyroidism may rarely be caused by a gain-of-function mutation in the TSH receptor, or by McCune-Albright syndrome. In such cases, newborn hyperthyroidism may be permanent (526).

XI. Thyroid Disease and Lactation

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QUESTION 87 - DOES MATERNAL THYROID HORMONE STATUS IMPACT LACTATION?

QUESTION 88- IN THE BREASTFEEDING MOTHER, SHOULD MATERNAL HYPOTHYROIDISM BE TREATED TO IMPROVE LACTATION?

QUESTION 89 - IN THE BREASTFEEDING MOTHER, SHOULD MATERNAL HYPERTHYROIDISM BE TREATED TO IMPROVE LACTATION?

Abnormal maternal thyroid hormone concentrations (both hypothyroidism and hyperthyroidism) can impact milk letdown and the ability to successfully breastfeed. While there are no controlled or randomized human trials, several case series and cohort analyses have been reported. One study reported 26 human pregnancies complicated by hypothyroidism in New Delhi, India. Deficient lactation was reported in 19.2% of subjects (527). Other case reports describe impaired lactation, which improved upon successful treatment of hypothyroidism (528). Interventional trials in non-human mammals corroborate these findings. Hapon and colleagues investigated the effects of PTU-induced hypothyroidism in rats at days 10-12 of lactation (529). After 30 minutes of suckling, milk excretion was reduced compared to euthyroid controls. The authors suggested mammary function was maintained while a reduced milk ejection reflex was likely responsible. A separate investigation of Brahman cows demonstrated reduced milk production in PTU-induced hypothyroid cows compared to euthyroid controls. Following cessation of PTU and normalization of thyroid status, lactation in these animals returned to baseline (530). Together, these data strongly suggest maternal hypothyroidism can adversely affect lactation. However, with limited human data and no controlled or randomized intervention studies, it is unclear what proportion of hypothyroid mothers would be affected. Furthermore, it is possible that many mothers experiencing only mild to moderate hypothyroidism could experience only minimal difficulties with breastfeeding and milk production. Importantly, the available data confirm that maternal hypothyroidism itself is not harmful to the breastfeeding infant *per se*, so long as adequate nutrition (milk) is provided. Therefore, it appears most reasonable to recommend evaluation of thyroid function in women who demonstrate poor lactation, with the goal of effectively returning any hypothyroid mother to a euthyroid state.

Maternal hyperthyroidism may also impair lactation, although the data are less clear. No controlled human trial or large cohort analysis has been performed. Two rat studies demonstrated adverse effects of hyperthyroidism on lactation. In one study, moderate to severe hyperthyroidism was induced in pregnant rats during and after pregnancy. Complete lactation failure was noted (531). A second study in which moderate hyperthyroidism was induced demonstrated continued ability of rats to lactate, but impairment of milk ejection. Ultimately, this resulted in death of the offspring due to malnutrition (532). Such limited data, obtained from only non-human populations, make it impossible to draw firm conclusions. Therefore, no recommendation can be made to treat maternal hyperthyroidism on the grounds that it will improve lactation.

- **Recommendation 74**

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As maternal hypothyroidism can adversely impact lactation, women experiencing poor lactation without other identified causes should have TSH measured to assess for thyroid dysfunction. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 75**
  Given its adverse impact upon milk production and letdown, subclinical and overt hypothyroidism should be treated in lactating women seeking to breastfeed. ***(Weak recommendation, Low quality evidence)***

- **Recommendation 76**
  The impact of maternal hyperthyroidism upon lactation is not well understood. Therefore, no recommendation to treat maternal hyperthyroidism on the grounds of improving lactation can be made at this time. ***(No recommendation, Insufficient Evidence)***

QUESTION 90 - IS MATERNAL THYROID HORMONE (THYROXINE OR LEVOTHYROXINE) TRANSFERRED TO THE NEWBORN VIA BREAST MILK?

A small amount of maternal thyroid hormone is present in the breast milk of lactating women, and also detected in cow, goat, and sheep milk. A study investigated thyroxine and triiodothyronine in the breast milk of mothers who delivered very premature infants. Thyroxine concentration in breast milk ranged from 0.17-1.83 mcg/L (mean 0.83mcg/L) (533). Assuming an average consumption of ~750 ml/day of breast milk, this equates to approximately 0.62 mcg of thyroxine per day. Assuming total thyroxine requirements of 40-60 mcg/day for most athyreotic infants, the amount of thyroxine transferred to the infant via the human lactating breast is ~1% of the total daily requirement. Thus, maternal transfer of thyroid hormone does not have a meaningful impact on the infant's thyroid hormone status.

Studies in cows (534), sheep (535), and donkeys (536) similarly find a small but detectable concentration of thyroxine and trioiodothyronine in the milk supply. One study demonstrated secretion of 200-300 pg/mL of T3 in cow milk. This translates into a total daily consumption of 0.2-0.4 mcg/day depending the age and feeding habits of the infant. Similarly, thyroxine concentrations in cows' milk demonstrate an average concentration of 0.97 ng/mL, translating into the consumption of approximately 0.75-1.5 mcg thyroxine per day. Thus, dairy milk obtained from cows, sheep, goats, or donkeys has little impact on the thyroid health of the infant or young child.

QUESTION 91 - SHOULD DIAGNOSTIC OR THERAPEUTIC RADIOPHARMACEUTICALS BE ADMINISTERED TO BREASTFEEDING OR LACTATING WOMEN?

Because radioactive iodine is concentrated in breast milk, and the half-life of ^{131}I is relatively long with ~8 days, use of ^{131}Ifor scanning or treatment is absolutely contraindicated in the breastfeeding mother. The half-life of ^{123}I is 13 hours. If circumstances necessitate the use of ^{123}I for of thyroid uptake measurement or scans while lactating, breast milk should be pumped and discarded for several days until the radioactive iodine has cleared from the body (537).

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- **Recommendation 77**
  The use of ^{131}I is contraindicated during lactation. If required, ^{123}I can be used if breast milk is pumped and discarded for 3-4 days before breastfeeding is resumed. Similarly, Tc-99m pertechnetate administration requires breast milk to be pumped and discarded during the day of testing. ***(Strong recommendation, Moderate quality evidence)***

QUESTION 92 - ARE ANTITHYROID MEDICATIONS (PTU, MMI) TRANSFERRED INTO BREAST MILK, AND WHAT ARE THE CLINICAL CONSEQUENCES TO THE BREASTFED INFANT?

Both PTU and MMI can be detected in the breast milk of treated hyperthyroid women. This finding raised initial concern that consumption of these medications could prove detrimental to the health of the breastfeeding infant. However, studies first performed using PTU confirmed that only a very small amount of the drug is transferred from maternal serum into breast milk. In a study of nine women given 200 mg PTU orally, milk PTU concentration was measured for four hours thereafter and only 0.007-0.077% of the ingested dose was detected. The authors calculated that a lactating mother consuming PTU 200 mg three times daily would transmit only 149 mcg (0.149 mg) of PTU daily to her infant (538). This is well below a therapeutic dose, and deemed to pose no risk to the breastfeeding infant. Separate studies confirm normal thyroid function in breastfed infants of mothers consuming PTU (539,540). In these studies, two infants were found to have an elevated TSH within one week of birth, however, these values normalized thereafter despite continued breastfeeding. This suggests the cause of neonatal hypothyroidism in these infants was transplacental passage of PTU before birth, as opposed to any adverse effect of PTU transferred via breast milk. The remaining children who consumed breast milk expressed from mothers taking PTU had normal thyroid function.

Studies of MMI or CM, confirm a 4-7 fold higher proportion of the medication transferred into maternal milk in comparison to PTU. Approximately 0.1-0.2% of an orally administered MMI/CM dose is excreted into breast milk (541,542). Johansen and colleagues calculated that a single 40 mg dose of MMI could result in delivery of 70 mcg (0.07 mg) to the breastfeeding infant. Several studies have separately investigated the effect of maternally ingested MMI or CM upon the thyroid status of the breastfeeding infant (543,544,545). Virtually all have documented normal neonatal thyroid function. Furthermore, several women overtreated with MMI/CM were found to have elevated TSH concentrations (TSH 19-102 mU/L). Even in these situations, normal neonatal thyroid function was nonetheless confirmed in breastfeeding infants.

The largest study investigating the effects of maternal MMI consumption during lactation was performed by Azizi and colleagues (545). Importantly, this study assessed both neonatal thyroid function in the breastfeeding offspring, but also intellectual development and physical growth in a subset of infants. Verbal and performance IQ scores were measured in 14 children who breastfed from MMI-treated mothers, with comparison to 17 control children. Testing was performed between 48-74 months of age. No difference was detected in the IQ or physical development of the breastfeeding children compared to the control children (543).

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Together, these data have led experts to confirm the safety of low to moderate doses of both PTU and MMI/CM in breastfeeding infants. However, given the relatively small size of the studied population, maximal daily doses of 20 mg MMI or 450 mg PTU are advised (352).

QUESTION 93 - WHAT IS THE APPROACH TO THE MEDICAL TREATMENT OF MATERNAL HYPERTHYROIDISM IN LACTATING WOMEN?

- **Recommendation 78**
  Excepting treatment decisions specifically made on the grounds of improving lactation (discussed above), the decision to treat hyperthyroidism in lactating women should be guided by the same principles applied to non-lactating women. ***(Strong recommendation, Low quality evidence)***

QUESTION 94 - WHEN MEDICAL TREATMENT OF MATERNAL HYPERTHYROIDISM IS INDICATED, WHAT MEDICATIONS SHOULD BE ADMINISTERED?

- **Recommendation 79**
  When antithyroid medication is indicated for women who are lactating, both MMI (up to maximal dose of 20 mg daily) and PTU (up to maximal dose of 450 mg daily) can be administered. Given a small, but detectable amount of both PTU and MMI transferred into breast milk, the lowest effective does of MMI/CM or PTU should always be administered**.** ***(Strong recommendation, Moderate quality evidence)***

QUESTION 95 - HOW SHOULD BREASTFEEDING CHILDREN OF MOTHERS WHO ARE TREATED WITH ANTITHYROID MEDICATIONS BE MONITORED?

- **Recommendation 80**
  Breastfed children of women who are treated with antithyroid drugs should be monitored for appropriate growth and development during routine pediatric health and wellness evaluations. Routine assessment of serum thyroid function in the child is not recommended. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 96 - WHAT ARE THE IODINE NUTRITIONAL CONSIDERATIONS IN LACTATING WOMEN?

Iodine is an essential nutrient required for thyroid hormone production and is primarily derived from the diet. For most breastfeeding infants, breast milk is the sole (or primary) source of nutrition, and thus of dietary iodine. Therefore, adequate iodine intake in the lactating mother positively impacts infant health. Iodine requirements increase during pregnancy to accommodate the maternal-fetal unit. Postpartum, maternal iodine requirements increase even further, as iodine is transferred to the breast feeding infant. The Institute of Medicine recommended dietary goals for individual total daily iodine intake (dietary and supplement) are 290 mcg/d for women

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who are breastfeeding (546). The World Health Organization recommends 250 mcg/d for both pregnant women and lactating women (547).

As discussed in section IV, dietary sources of iodine vary regionally, and the dietary iodine intake of individuals cannot be reliably ascertained either by patient history or by any laboratory measure. Due to concerns that a portion of women in the United States are mildly to moderately iodine deficient (which can be exacerbated during lactation due to increased demand), iodine supplementation for breastfeeding mothers is recommended. The ATA has previously recommended 150 mcg daily as iodine supplementation for all North American women who are breastfeeding (117). The goal of supplementation is to augment, rather than replace, dietary iodine intake.

Unfortunately, recommendations for iodine supplementation when breastfeeding have not seen widespread adoption. In the NHANES 2001-2006 survey, only 15% of lactating women reported ingesting iodine-containing supplements (121). Furthermore, one analysis confirmed that only 51% of U.S. prenatal vitamins contained iodine (122). Therefore, physician counseling at the time of post-birth hospital discharge is paramount.

- **Recommendation 81**
  All breastfeeding women should ingest approximately 250 mcg of dietary iodine daily. ***(Strong recommendation, High quality evidence)***

- **Recommendation 82**
  Breastfeeding women should supplement their diet with a daily oral supplement that contains 150 mcg of iodine. This is optimally delivered in the form of potassium iodide (present in a multivitamin) because kelp and other forms of seaweed do not provide a consistent delivery of daily iodine. ***(Strong recommendation, Moderate quality evidence)***

- **Recommendation 83**
  In severely iodine deficient, low-resource regions, where universal salt iodization is lacking and daily supplementation is not feasible, lactating women should receive one dose of 400 mg iodine as oral iodized oil soon after delivery. ***(Strong recommendation, High quality evidence)***

- **Recommendation 84**
  As is the case during pregnancy, sustained iodine intake while breastfeeding that exceeds 500-1100 mcg daily should be avoided due to concerns about the potential for inducing hypothyroidism in the infant. ***(Strong recommendation, Moderate quality evidence)***

XII. Postpartum thyroiditis

QUESTION 97- WHAT IS THE DEFINITION OF POSTPARTUM THYROIDITIS AND WHAT ARE ITS CLINICAL IMPLICATIONS?

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Postpartum thyroiditis is the occurrence of thyroid dysfunction, excluding Graves' disease, in the first postpartum year in women who were euthyroid prior to pregnancy (548). This is an inflammatory autoimmune condition. In the classic form, transient thyrotoxicosis is followed by transient hypothyroidism with a return to the euthyroid state by the end of the initial postpartum year (2). The clinical course of PPT varies, with approximately one quarter of patients presenting with the classical form, one quarter with isolated thyrotoxicosis, and one-half presenting with isolated hypothyroidism (431). The thyrotoxic phase of PPT typically occurs between 2-6 months postpartum, but episodes have been reported as late as one year following delivery. All episodes of thyrotoxicosis resolve spontaneously. The hypothyroid phase of PPT occurs from 3 to 12 months postpartum with 10-20% of cases resulting in permanent hypothyroidism. It should be noted however, that a prospective study reported that 50% of women with PPT remained hypothyroid at the end of the first postpartum year (549).

QUESTION 98 - WHAT IS THE ETIOLOGY OF POSTPARTUM THYROIDITIS?

Postpartum thyroiditis is an autoimmune disorder associated with the presence of thyroid antibodies (thyroid peroxidase and thyroglobulin antibodies), lymphocyte abnormalities, complement activation, increased levels of IgG1, increased NK cell activity, and specific HLA haplotypes (550,551,552). Women who are thyroid antibody positive in the first trimester have a high risk of developing PPT, ranging from 33-50% (553). Women with the highest antibody titers also have the highest risk of PPT (431). The occurrence of PPT reflects the rebound of the immune system in the postpartum period after the relative immune suppression of pregnancy.

QUESTION 99 - HOW SHOULD THE ETIOLOGY OF NEW THYROTOXICOSIS BE DETERMINED IN THE POSTPARTUM PERIOD?

The major challenge is to differentiate thyrotoxicosis caused by PPT from thyrotoxicosis caused by Graves' disease. This is an important distinction, as the two disease entities require different treatments and have markedly different clinical courses. The timing of onset provides some clues about etiology. In a Japanese hospital study of 42 patients who developed thyrotoxicosis within the first year after pregnancy, 86% of patients who had debut of disease within the first 3 months after delivery had thyroiditis, whereas all who developed thyrotoxicosis after 6.5 months had Graves' disease (554).

TSH receptor antibodies are positive in Graves' disease in nearly all cases and are typically negative in PPT, although some mixed-type disease is seen. An elevated T4:T3 ratio suggests the presence of PPT. Physical stigmata of Graves' disease, such as goiter with a bruit or ophthalmopathy, are diagnostic when present. The radioiodine uptake is elevated or normal in Graves' disease and low in the thyrotoxic phase of PPT, but the use of radioactive diagnostic procedures in lactating patients is rarely indicated. Due to their short half-lives, ^{123}I or technetium scans (Tc-99m) may be used in women who are breastfeeding if breast milk is pumped and discarded for several days after the scan pending the isotope used (see Section XI). As described in Section XI, the use of ^{131}I is contraindicated in women who are breastfeeding.

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QUESTION 100 - WHAT IS THE PREVALENCE OF POSTPARTUM THYROIDITIS?

The prevalence of PPT is approximately 5%, although it has varied markedly in different studies, with frequencies reported from 1.1%-16.7% (555). Women with other autoimmune disorders have an increased risk of PPT. Specifically, the prevalence of PPT is 3-4 times higher in women with diabetes mellitus type 1 compared to unselected populations (556,557). The frequency of PPT is 25% in women with chronic viral hepatitis (558), 14% in women with systemic lupus erythematosus (559), 44% in women with a prior history of Graves' disease (560), and 27 % in patients with anti-pituitary antibodies (561). Individuals who recover fully from PPT have a 70% chance of developing PPT in each subsequent pregnancy (562). Women on levothyroxine therapy secondary to Hashimoto's thyroiditis may develop PPT if their thyroid gland is not completely atrophic (563). Cases of PPT have been reported following pregnancy loss, but the prevalence of PPT following pregnancy loss is unknown (564).

QUESTION 101 - WHAT SYMPTOMS ARE ASSOCIATED WITH POSTPARTUM THYROIDITIS?

Postpartum thyroiditis is a painless condition and most women are asymptomatic or only mildly symptomatic during the thyrotoxic phase. This is due to the fact that the degree of increase in thyroid hormones is typically mild, and T4 levels are usually more elevated than T3. Nevertheless, in prospective studies, reported symptoms include irritability, heat intolerance, fatigue, and palpitations (431,565,566,567). The hypothyroid phase of PPT is more frequently symptomatic. Symptoms during the hypothyroid phase of PPT may include cold intolerance, dry skin, fatigue, impaired concentration, and paresthesias (566,567). One study demonstrated that patients with TPO antibodies and PPT had more symptoms that those who were TPO antibody negative (568).

QUESTION 102 - IS POSTPARTUM THYROIDITIS ASSOCIATED WITH DEPRESSION?

Studies evaluating the relationship of PPT to postpartum depression have been inconsistent (569,570,571,572,573). Two studies have reported a significant association between the presence of thyroid antibodies and depression (568,574), irrespective of thyroid function, whereas another study showed no association between the presence of microsomal antibodies and postpartum depression (575). A prospective trial of levothyroxine treatment versus placebo in postpartum TPO antibody positive women resulted in no difference in rates of postpartum depression between the two groups (576).

- **Recommendation 85**
  All patients with depression, including postpartum depression, should be screened for thyroid dysfunction. ***(Strong recommendation, Low quality evidence)***

QUESTION 103 - WHAT IS THE TREATMENT FOR THE THYROTOXIC PHASE OF POSTPARTUM THYROIDITIS?

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There have been no prospective studies evaluating when and how to treat PPT. Treatment of the thyrotoxic phase is guided by its transitory nature. Antithyroid drugs (PTU and MMI) are ineffective in treating the thyrotoxic phase of PPT as it is a destructive thyroiditis in which thyroid hormone synthesis is not increased. Symptoms are typically mild. In rare cases when symptoms are clinically significant, propranolol at the lowest possible dose to alleviate symptoms may be used. The thyrotoxic phase of PPT must be differentiated from recurrent or *de novo* Graves' disease.

- **Recommendation 86**
  During the thyrotoxic phase of PPT, symptomatic women may be treated with beta-blockers. A beta-blocker which is safe for lactating women, such as Propranolol or Metoprolol, at the lowest possible dose to alleviate symptoms is the treatment of choice. Therapy is typically required for a few weeks. (***Strong recommendation, Moderate quality evidence)***

- **Recommendation 87**
  Antithyroid drugs are not recommended for the treatment of the thyrotoxic phase of PPT. (***Strong recommendation, High quality evidence)***

QUESTION 104 - ONCE THE THYROTOXIC PHASE OF POSTPARTUM THYROIDITIS RESOLVES, HOW OFTEN SHOULD TSH BE MEASURED TO SCREEN FOR THE HYPOTHYROID PHASE?

- **Recommendation 88**
  Following the resolution of the thyrotoxic phase of PPT, serum TSH should be measured in approximately 4-8 weeks (or if new symptoms develop) to screen for the hypothyroid phase. ***(Strong recommendation, High quality evidence)***

QUESTION 105 - WHAT IS THE TREATMENT FOR THE HYPOTHYROID PHASE OF POSTPARTUM THYROIDITIS?

In women with significant symptoms, those currently lactating or women who are actively attempting pregnancy, treatment should be started (431). Levothyroxine treatment should be considered during the hypothyroid phase of PPT if the patient is mildly symptomatic, or recommended if the patient is considering another conception. If treatment is delayed, thyroid function should be re-checked every 4-8 weeks until euthyroidism is restored and women should be counseled to use contraception.

- **Recommendation 89**
  Levothyroxine should be considered for women with symptomatic hypothyroidism due to PPT. If treatment is not initiated, their TSH level should be repeated every 4-8 weeks until thyroid function normalizes. Levothyroxine should also be started in hypothyroid women who are attempting pregnancy or who are breastfeeding. ***(Weak recommendation, Moderate quality evidence)***

QUESTION 106 - HOW LONG SHOULD LEVOTHYROXINE BE CONTINUED ONCE INITIATED?

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The length of time that levothyroxine should be continued has not been systematically evaluated. Guiding principles are to maintain a euthyroid state in women who are attempting pregnancy or pregnant. Tapering levothyroxine doses in order to determine whether the hypothyroid phase of PPT was transitory or permanent can begin by 12 months postpartum. Tapering should be gradual and TSH should be monitored every 6-8 weeks.

- **Recommendation 90**
  If levothyroxine is initiated for PPT, discontinuation of therapy should be attempted after 12 months. Tapering of levothyroxine should be avoided when a woman is actively attempting pregnancy or is pregnant. ***(Weak recommendation, Low quality evidence)***

QUESTION 107 - HOW OFTEN SHOULD THYROID FUNCTION TESTING BE PERFORMED AFTER THE HYPOTHYROID PHASE OF POSTPARTUM THYROIDITIS RESOLVES?

The impact of PPT on long-term thyroid function has been evaluated in seven studies (549,562,577,578,579,580,581). These data demonstrate that 10-50% of women in whom the hypothyroid phase of PPT initially resolves will ultimately go on to develop permanent hypothyroidism. Factors associated with an increased risk of developing permanent hypothyroidism are multiparity, thyroid hypoechogenicity on ultrasound, greater severity of the initial hypothyroidism, higher thyroid peroxidase antibody titers, greater maternal age, and a history of pregnancy loss.

- **Recommendation 91**
  Women with a prior history of PPT should have TSH testing annually to evaluate for the development of permanent hypothyroidism. ***(Strong recommendation, High quality evidence)***

QUESTION 108 - DOES TREATMENT OF THYROID ANTIBODY POSITIVE EUTHYROID WOMEN DURING PREGNANCY PREVENT POSTPARTUM THYROIDITIS?

Two randomized placebo-controlled controlled trials have evaluated the efficacy of iodine or levothyroxine treatment during pregnancy to prevent the development of PPT in thyroid antibody positive women. Neither intervention decreased the incidence of PPT (154,582). A single trial has suggested a benefit of selenium supplementation for the prevention of PPT in TPO antibody positive pregnant women, though this has not been independently validated. Furthermore, selenium use has been associated with an increased risk of type 2 diabetes (156). Currently there is not sufficient evidence to recommend selenium supplementation during pregnancy in thyroid antibody positive women (see Recommendation 12).

- **Recommendation 92**

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Treatment of euthyroid thyroid antibody positive pregnant woman with either levothyroxine or iodine to prevent PPT is ineffective and is not recommended. ***(Strong recommendation, High quality evidence)***

XIII. Screening for Thyroid Dysfunction Before or During Pregnancy

Whether to universally screen for thyroid disease either before or during pregnancy remains controversial. For universal screening to be recommended, any index condition must be prevalent, associated with adverse health outcomes, and treatable. Furthermore, effective therapy must exist, but also be practical and effectively deliverable. Finally, screening must be cost-effective.

Screening for thyroid dysfunction in pregnancy fulfills some of these criteria. Hypothyroidism, hyperthyroidism, and thyroid autoimmunity are common conditions, with prevalence rates of 2-3% (259,260,289,583), 0.1-0.4% (397) and up to17% (137) respectively. Untreated overt hypothyroidism and hyperthyroidism are associated with adverse obstetrical and fetal outcomes. Among overtly hypothyroid, but undiagnosed pregnant women, the majority will remain hypothyroid following pregnancy, with a mean time to diagnosis in one study of 5 years (276). However, overt thyroid dysfunction is less common than subclinical dysfunction and is frequently identified by clinical assessment at the time of presentation. Mild TSH suppression can be seen in normal early pregnancy and, even when TSH is ≤ 2.5% of the gestational reference range in association with normal Free T4 (cutoff between 0.008 and 0.668 mU/L, depending on the gestational age), it is not associated with adverse obstetrical outcomes (22). Thus, the most notable impact of a universal screening mandate for thyroid dysfunction would be the identification of the large proportion of patients with subclinical hypothyroidism (mild elevations in serum TSH with normal thyroid hormone levels).

Presently, most studies investigating subclinical hypothyroidism suggest an association with adverse obstetrical outcomes that is linear, as greater degrees of TSH elevation are associated with increased risks to the pregnancy. Such adverse outcomes also appear to be influenced by concomitant anti-thyroid autoimmunity. Exemplifying this, a large prospective study of 3315 women demonstrated the additive effect of anti-TPO positivity to the degree of TSH elevation. In anti-TPO positive women the risk of pregnancy loss increased significantly beyond a TSH concentration > 2.5 mU/L (OR 4.95 for TSH 2.5-5.2), with an even greater increase when TSH was > 5.2 mU/L (OR 9.56 for TSH 5.2-10 mU/L), whereas in anti-TPO negative women, significant increases in risk of pregnancy loss was identified only when TSH concentrations exceeded 5.2 mU/L (OR 3.4 for TSH 5.2-10) (288).

Thyroid status can be accurately assessed with currently available blood tests, including TSH, TT4/Free T4, and TPOAb. These tests are relatively inexpensive and widely available. Thus, the principal complexity surrounding the screening question relates to the evidence for treatment effectiveness, especially in the population of pregnant women with subclinical

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hypothyroidism. While prior retrospective studies have suggested a benefit of levothyroxine treatment in this population (276,277), such findings have not been sufficiently replicated in blinded, prospective analyses thus far.

Important to this discussion is the understanding of two different adverse endpoints that must be considered. These endpoints are maternal/pregnancy risk (primarily pregnancy loss), and separately the adverse effects on fetal neurocognitive development as manifested by lower IQ in the offspring. These endpoints do not necessarily co-segregate. Therefore, each must be considered separately, as different interventions and their timing may affect such endpoints discordantly.

QUESTION 109 - DOES IDENTIFICATION AND LEVOTHYROXINE TREATMENT OF WOMEN WITH SUBCLINICAL HYPOTHYROIDISM OR THYROID AUTOIMMUNITY REDUCE PREGNANCY COMPLICATIONS AND PREGNANCY LOSS?

Retrospective studies have frequently suggested a positive correlation between treatment of mild elevations of maternal serum TSH and decreased risk of pregnancy loss. For example, a retrospective study from Belgium assessed the effect of TSH screening in a small cohort of pregnant women. Levothyroxine treatment of TPOAb positive women with TSH > 1 mU/L led to a reduction of pregnancy loss rates from 16% to 0% (180). A separate historical cohort analysis studied >1000 pregnant women in the United Kingdom treated with long-term levothyroxine. Pregnancy loss rates were significantly higher when TSH was > 4.5 mU/L (and especially when >10 mU/L) compared with when TSH was < 2.5 mU/L (318). The retrospective design and lack of TPO antibody data are two important limitations of this study.

Limited RCT data on the effects of treatment of subclinical hypothyroidism in pregnancy are available to date. Negro and colleagues randomized euthyroid (TSH <4.2 mU/L) TPOAb positive women to treatment with LT4 or no treatment. This intervention demonstrated a significant reduction in preterm deliveries (from 22% to 7%) and miscarriage rates (from 14% to 3.5%) (28). However, limitations of this study include its small sample size and the fact that average time of levothyroxine initiation was late in the first trimester (mean 10.3 weeks), at a time when many pregnancy losses had already occurred.

Two more recent prospective, RCTs have investigated the benefits of universal screening of pregnant women with subsequent levothyroxine treatment of women with TSH > 2.5 mU/L. Negro and colleagues randomized 4562 women to universal screening versus screening of women at high-risk for thyroid disease. Women identified to have TPOAb positivity and TSH concentrations > 2.5 mU/L were treated with levothyroxine. The timing of treatment initiation was 8.8 weeks gestation. Even though this is well into the first trimester, limiting assessment of the outcome, this is the earliest randomized intervention trial published to date. In the primary analysis, there was no significant difference in adverse events detected between the universally screened cohort versus those who underwent high-risk screening. The main limitation of this study was its design, as all high-risk patients were treated in both study arms, limiting the ability to detect a treatment effect. However, in a secondary analysis of the low-risk cohort, a significant decrease in adverse obstetrical and neonatal outcomes was detected when a screening and

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treatment strategy was applied (OR 0.43, CI 0.26-0.70) (584). How to best interpret this finding, however, remains unclear, as this study used a composite endpoint for assessing adverse outcomes. For these reasons, this study alone is often viewed as insufficient to warrant adoption of a universal screening mandate.

A second investigation employed cluster randomization at two centers in China, comparing a process of universal screening at one hospital (and treatment when TSH > 2.5 mU/L) to a traditional non-screening approach in the second institution. In the latter group, serum was obtained from women in early pregnancy, but banked and not analyzed until the postnatal period. The authors concluded that identifying and treating elevated TSH values early in pregnancy reduced pregnancy loss rates (OR 0.343, CI 0.21-0.56) and macrosomia (OR 0.46, CI 0.28-0.74) (585). However, these data should be viewed with caution as the timing of enrollment at the two centers varied substantially, likely influencing the reporting of pregnancy loss rates. Notably, the screening arm enrolled women at week 11 of pregnancy whereas the control arm enrolled women at week 7. As most pregnancy losses occur during the first trimester, the earlier time at testing in the control group suggests that the much higher rates of pregnancy loss were simply due to early enrollment bias.

Importantly, two additional prospective, randomized trials investigating obstetric outcomes are currently in progress. The Thyroid Antibodies and Levothyroxine Trial (586) is a large RCT conducted in the UK, randomizing euthyroid, TPOAb positive women with a history of pregnancy loss or infertility to treatment with 50 mcg levothyroxine versus placebo. The endpoint is successful delivery of the infant beyond 34 weeks of gestation. Separately, the T4Life trial in the Netherlands is randomizing euthyroid anti-TPO antibody positive women with a history of recurrent pregnancy losses to treatment with levothyroxine (starting before conception) versus placebo. The primary outcome is live birth after 24 weeks gestation (587).

QUESTION 110 - DOES IDENTIFICATION AND LEVOTHYROXINE TREATMENT OF PREGNANT WOMEN WITH SUBCLINICAL HYPOTHYROIDISM IMPROVE NEUROCOGNITIVE OUTCOMES IN OFFSPRING?

With regards to the endpoint of fetal neurocognitive development, there are mixed findings from currently available studies. Haddow and colleagues first published seminal data from a large case-control study investigating the effects of untreated maternal hypothyroidism on the IQ of offspring tested at ~8 years (276). This study analyzed sera from 25,216 women obtained at an average gestational age of 17 weeks. They identified 62 women with either TSH concentrations $\geq 99.7^{th}$ percentile, or women with TSH concentrations between the 98 and 99.6^{th} percentile who also had low FT4 concentrations. The authors compared the IQ of the offspring (at 7-9 years) with that of 124 matched children born to euthyroid mothers. IQ scores were 7 points lower in children born to untreated, hypothyroid mothers in comparison to controls. However, the retrospective nature of this study has led to questions regarding its reproducibility.

The largest prospective randomized trial of levothyroxine therapy investigating the treatment of maternal hypothyroidism or hypothyroxinemia in early pregnancy is the CATS study. This study randomized 22,000 women with singleton pregnancies at <16 weeks gestation

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to immediate thyroid function testing and levothyroxine treatment if serum TSH was >97.5th percentile and/or if serum FT4 was <2.5th percentile. The control arm received no treatment, though serum was obtained in early pregnancy and banked until testing was performed postpartum. The primary outcome was offspring IQ at 3 years of age. Ultimately, the trial found no significant difference in IQ between the children of 390 treated mothers compared with those of 404 untreated mothers (306). Limitations of this study include the timing of levothyroxine administration (median initiation >13 weeks), and the mild degree of TSH elevation (median TSH 3.1-3.8 mU/L) in its subjects. Furthermore, the predictive value of early IQ testing at age 3 years remains uncertain. With these major limitations, the negative primary endpoint nonetheless does not support universal screening for thyroid disease in pregnant women.

Two separate randomized trials evaluating the effect of levothyroxine treatment upon fetal neurodevelopment are currently in progress. The first is a multicenter, randomized placebo-controlled clinical trial conducted by the National Institutes of Health, which seeks to evaluate the effects of LT4 treatment in women with either subclinical hypothyroidism or isolated hypothyroxinemia on offspring cognition. Preliminary results presented as an oral abstract at the 2016 Annual Meeting of the Society for Maternal Fetal Medicine meeting showed that initiation of levothyroxine treatment in these women at a mean gestational age of 17 weeks had no effect on child IQ (21). Full results are anticipated in 2017. A separate, large prospective study is also underway in China. The "Subclinical Hypothyroid during Early Pregnancy" (SHEP) trial will screen 21,500 women planning pregnancy and seek to assess the effects of levothyroxine treatment initiated before conception in women with iodine deficiency, those with subclinical hypothyroidism, and those positive for TPOAb (588). The results of the study are expected between 2018-2020.

Importantly, if a screening paradigm is conclusively proved effective, universal screening of women in the first trimester has been shown to be cost-effective (589,590,591,592). A study by Dosiou et al. established the cost-effectiveness of universal screening of pregnant women with both TSH and TPO antibodies in the first trimester, when compared with a strategy of high-risk screening (590). At base-case analysis, this study assumed that treatment of identified women with TPO positivity and subclinical hypothyroidism reduced pregnancy loss and preterm delivery rates as per the randomized clinical trial of Negro and colleagues (28), and that screening resulted in more prompt diagnosis of PPT and hypothyroidism later in life, in the women who developed these disorders. The study did not assume any adverse effects of untreated thyroid disease on child IQ. In sensitivity analyses, even when the benefits of screening were limited to detection and treatment of overt hypothyroidism, screening was shown to be highly cost-effective at < $8000/quality-adjusted life year (QALY). Assumption of benefit for fetal IQ made screening cost-saving. Another recent study from Spain demonstrated similar findings, with an incremental cost-effectiveness ratio of €374.28/QALY (592). The cost-effectiveness of screening for thyroid disease in pregnancy compares well with that for other widely used screening practices in pregnant women such as cystic fibrosis screening ($8290/QALY) (593) and prenatal diabetes screening ($16,689-19,339/QALY) (594).

Finally, it is important to place the screening discussion in the context of worldwide opinion, and acknowledge the recommendations of other Societies. The 2011 ATA pregnancy guidelines and the 2012 Endocrine Society pregnancy guidelines significantly expanded the definition of "high risk" women from that used in earlier editions to include women > 30 years

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of age. This expanded definition of "high risk" encompassed many more women in populations with a high mean maternal pregnancy age. In a 2012 study by Potlukova et al., with a mean maternal age at pregnancy of 31 years, the addition of age 30 or older as a risk factor increased the proportion of women correctly identified in a case-finding strategy from 55.3% to 85.6% (595). However, in a recent Chinese population with mean maternal age at pregnancy of 26.6 years, testing using only high-risk criteria missed 82.4% of women with subclinical hypothyroidism, 28.6% of women with overt hyperthyroidism and 74.6% of women with anti-thyroid antibodies (596). Member surveys of professional societies have shown that 42.7% of responders in Latin America and 43% in Europe perform universal screening (597,598), whereas only 21% of the Asia-Oceania Thyroid Associan members do so (599), and 74% of ATA members support such an approach (600). In the recent 2014 ETA guidelines, the majority of authors recommended universal screening because of the beneficial effects of treatment for overt hypothyroidism, and the fact that the targeted approach will miss a large percentage of women with subclinical hypothyroidism (601). The Spanish Society of Endocrinology and Nutrition (602) and the Indian Thyroid Society (603), have expressed support for universal screening in early pregnancy or preconception. The Indian National Guidelines recommend testing only high-risk women (604). Finally, the American Society for Reproductive Medicine recommends TSH testing in all infertile women attempting pregnancy and in "high-risk women" in early pregnancy (605).

Together, these data provide a perplexing dilemma. Studies strongly suggest an increase in pregnancy loss risk associated with elevated maternal TSH concentrations, especially when elevated TPOAb are detected. Similarly, thyroid dysfunction is a prevalent condition that can be diagnosed with readily available and inexpensive tests. However, the effectiveness of levothyroxine therapy has not yet been conclusively demonstrated. Importantly, many have argued that screening for thyroid dysfunction must occur very early in pregnancy (e.g. 4-7 weeks of gestation) to maximize potential benefits of levothyroxine treatment upon pregnancy loss rates and possibly neurocognitive development. The largest prospective screening studies thus far have provided data most translatable to typical pregnancy care currently provided worldwide, with initial evaluation between 10-15 weeks of gestation. This is important to consider, as the feasibility of any screening earlier in gestation is unclear.

Further uncertainty surrounds the choice of biochemical test to use for any screening mandate. Most studies identify two dichotomous hypothyroid populations detected in early pregnancy– those with elevated maternal TSH concentrations, but separately those with decreased free T4 concentrations. Such populations rarely overlap. These findings suggest that the most effective screening strategies may require multi-modal testing beyond just TSH evaluation. And, as mentioned above, detection of elevated TPOAb concentrations may ultimately prove the strongest risk factor for adverse outcomes, though no RCT to date has used this as the sole initial testing approach. Furthermore, the only study to date to target treatment of pregnant women with low FT4 concentrations demonstrated no benefit (306).

Therefore, while acknowledging an impressive amount of retrospective data associating thyroid dysfunction with pregnancy harm, the above uncertainties preclude the task force from recommending for or against a universal screening mandate. The outcome of future studies will prove critical for expanding our knowledge, and the task force acknowledged the wealth of data, which will become available in the years ahead. In coming to this conclusion, the task force

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noted that the majority of patients identified through any universal screening process have TSH concentrations between 2.5-5.0 mU/L – a population in whom a treatment benefit is not well established. Furthermore, such a strategy could have detrimental effects, labeling many patients with a biochemical abnormality, and in many cases leading to initiation of possibly inappropriate long-term treatment.

One task force member (CD) dissented from this recommendation, feeling that universal testing for maternal TSH and anti-TPO antibodies soon after pregnancy confirmation is warranted given the existing support for the obstetrical benefits of treatment, with minimal risk of harm with appropriate monitoring. There might be an additional benefit of treatment on fetal neurodevelopment, as shown in animal studies. Unfortunately, the timing of initiation of levothyroxine treatment after completion of the first trimester in the RCTs that examine child IQ as the outcome is a very serious design flaw that biases these studies to producing negative results, since they miss the relevant window of opportunity to influence neurodevelopment. Nonetheless, universal screening would allow identification and treatment of all women with overt hypothyroidism, which is prevalent in 0.3-0.5% of pregnant women (259,260,583) and asymptomatic in about 70% of patients (606). It would also allow identification and selective treatment of women with autoimmune subclinical hypothyroidism, and appropriate close monitoring of euthyroid women with isolated thyroid autoimmunity, some of whom will develop hypothyroidism during gestation or PPT.

The task force uniformly recommends that healthcare providers identify all newly pregnant women at high risk for thyroid disease. This would include women with a history of thyroid dysfunction, symptoms or signs of thyroid dysfunction, presence of a goiter, and known thyroid antibody positivity. Other risk factors for thyroid disease include age > 30 years (145,607), history of diabetes mellitus type 1 (608) or other autoimmune disorders (609), history of pregnancy loss, preterm delivery or infertility (206,208), history of head or neck radiation (610) or prior thyroid surgery (611,612), family history of autoimmune thyroid disease or thyroid dysfunction (613,614), morbid obesity (615,616), use of amiodarone (617), lithium (392), or recent administration of iodinated radiologic contrast (618), two or more prior pregnancies (619), and residing in area of moderate to severe iodine deficiency (620). In these women, measurement of serum TSH concentration should be performed as soon as pregnancy is confirmed, with reflex anti-TPO antibody if TSH is 2.5 – 10 mU/L (Figure 1).

While screening women for thyroid disease preconception may also prove beneficial, there are currently no data to support such an approach, and the process of testing such a high volume of women, the majority of whom will not become pregnant, seems impractical. Universal screening for TPOAb in early pregnancy or possibly preconception may also prove an attractive alternative, but warrants further investigation. The high prevalence of anti-TPO positivity (up to 17% in reproductive age women), the extensive findings demonstrating increased risks in the anti-TPO positive population, and the fact that this test would also identify women at risk for developing hypothyroidism during gestation (20%) (147) and PPT (30-50%) (621), make this test an attractive theoretical consideration. However, no data support this testing algorithm at present.

QUESTION 111 – SHOULD WOMEN BE UNIVERSALLY TESTED FOR THYROID FUNCTION BEFORE OR DURING PREGNANCY?

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- **Recommendation 93**
  There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy. ***(No recommendation, Insufficient evidence***)

- **Recommendation 94**
  There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have positive TPOAb. ***(No recommendation, Insufficient evidence)***

- **Recommendation 95**
  Universal screening to detect low free thyroxine concentrations in pregnant women is not recommended. ***(Weak recommendation, Moderate quality evidence)***

- **Recommendation 96**
  All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or anti-thyroid medications (MMI, CM, or PTU). ***(Strong recommendation, High quality evidence)***

- **Recommendation 97**
  All patients seeking pregnancy, or newly pregnant, should undergo clinical evaluation. If any of the following risk factors are identified, testing for serum TSH is recommended.
  1. A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
  2. Known thyroid antibody positivity or presence of a goiter
  3. History of head or neck radiation or prior thyroid surgery
  4. Age >30 years
  5. Type 1 diabetes or other autoimmune disorders
  6. History of pregnancy loss, preterm delivery, or infertility
  7. Multiple prior pregnancies (≥ 2)
  8. Family history of autoimmune thyroid disease or thyroid dysfunction
  9. Morbid obesity (BMI ≥ 40 kg/m2)
  10. Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
  11. Residing in an area of known moderate to severe iodine insufficiency

  (Strong recommendation, Moderate quality evidence)

XIV. Future Research Directions

In developing the Guidelines, the task force frequently struggled with the paucity of high-quality double-blinded placebo-controlled trials in the field of thyroid and pregnancy. In fact, only a minority of the 98 recommendations (24%) in the present Guidelines were graded at the

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highest American College of Physicians Grading System level of evidence. The Guidelines task force identified topics for future research that will be critical in resolving many of the unanswered questions in the field of thyroid and pregnancy. Of concern to the task force is that most of the double-blind placebo-controlled studies either recently completed, or presently underway, began screening and intervention after the first trimester. As such, these studies will not be able to address the impact of levothyroxine treatment in the first trimester in women with subclinical hypothyroidism, isolated hypothyroxinemia, or thyroid antibody positivity on the mother and developing fetus. A trial which screens women pre-conception and then randomizes women with subclinical hypothyroidism, isolated hypothyroxinemia and isolated thyroid autoimmunity (with normal TSH) to either a treatment or no treatment arm is needed. The task force is aware of the difficulties inherent in performing such a trial, and the ethical challenges to be faced. Nevertheless, we believe that such a trial is feasible, can be ethically performed with appropriate study design and safeguards, and will yield invaluable information related to the optimal care of the pregnant women and the developing fetus. Other areas for future research include:

- A study evaluating the impact of iodine supplementation in pregnant women with the mildest form of iodine deficiency (median urinary iodine concentrations 100-150 μg/L).
- A RCT of early levothyroxine intervention (at 4-8 weeks) in women with either subclinical hypothyroidism or isolated hypothyroxinemia to determine effects on child IQ.
- A study focused on the effects of iodine supplementation during lactation on infant thyroid function and cognition.
- A study to determine safe upper limits for iodine ingestion in pregnancy and lactation.
- A comprehensive study to assess the iodine status of pregnant and lactating women in the United States.
- A trial assessing the optimal targeted free T4 level in pregnant women treated for hyperthyroidism.
- Another well powered, prospective, randomized interventional trial of levothyroxine in euthyroid patients who are anti-TPO positive for the prevention of miscarriage and preterm delivery.
- A study to evaluate the impact of levothyroxine therapy in euthyroid thyroid antibody positive women with recurrent pregnancy loss.
- Basic and clinical studies aimed at elucidating the mechanisms underlying thyroid antibody-associated adverse pregnancy outcomes.
- Studies examining the effects of TGAb on pregnancy outcomes.
- A study investigating the best criteria that can be used to predict which patients with hyperthyroidism can safely tapered off antithyroid medication in the first trimester
- A study evaluating the safest timing of administration of the different antithyroid drugs for management of hyperthyroidism in pregnancy.
- Novel ways to differentiate fetal hyperthyroidism from fetal hypothyroidism when a fetal goiter is detected.

XV. Disclosure Statement

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TABLE 1. RECOMMENDATIONS (FOR THERAPEUTIC INTERVENTIONS) BASED ON STRENGTH OF EVIDENCE

Recommendation and evidence quality	***Description of supporting evidence***[a]	***Interpretation***
Strong recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Can apply to most patients in most circumstances without reservation
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Can apply to most patients in most circumstances without reservation
Low-quality evidence	Observational studies/case studies	May change when higher-quality evidence becomes available
Weak recommendation		
High-quality evidence	RCT without important limitations or overwhelming evidence from observational studies	Best action may differ based on circumstances or patients' values
Moderate-quality evidence	RCT with important limitations or strong evidence from observational studies	Best action may differ based on circumstances or patients' values
Low-quality evidence	Observational studies/case studies	Other alternatives may be equally reasonable
Insufficient	Evidence is conflicting, of poor quality, or lacking	Insufficient evidence to recommend for or against

[a]This description of supporting evidence refers to therapy, therapeutic strategy, or prevention studies. The description of supporting evidence is different for diagnostic accuracy studies.
RCT, randomized controlled trial.

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TABLE 2. RECOMMENDATIONS (FOR DIAGNOSTIC INTERVENTIONS) BASED ON STRENGTH OF EVIDENCE

Recommendation and evidence quality	***Methodologic quality of supporting evidence***	***Interpretation***
Strong recommendation		
High-quality evidence	Evidence from one or more well-designed nonrandomized diagnostic accuracy studies (i.e., observational—cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results)	Implies the test can be offered to most patients in most applicable circumstances without reservation.
Moderate-quality evidence	Evidence from nonrandomized diagnostic accuracy studies (cross-sectional or cohort), with one or more possible limitations causing minor concern about internal validity or external generalizability of the results	Implies the test can be offered to most patients in most applicable circumstances without reservation.
Low-quality evidence	Evidence from nonrandomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results	Implies the test can be offered to most patients in most applicable circumstances, but the utilization of the test may change when higher-quality evidence becomes available.
Weak recommendation		
High-quality evidence	Evidence from one or more well-designed nonrandomized diagnostic accuracy studies (i.e., observational—cross-sectional or cohort) or systematic reviews/meta-analyses of such observational studies (with no concern about internal validity or external generalizability of the results)	The degree to which the diagnostic test is seriously considered may differ depending on circumstances or patients' or societal values.
Moderate-quality evidence	Evidence from nonrandomized diagnostic accuracy studies (cross-sectional or cohort), with one or more possible limitations causing minor concern about internal validity or external generalizability of the results	The degree to which the diagnostic test is seriously considered may differ depending on individual patients'/practice circumstances or patients' or societal values.
Low-quality evidence	Evidence from nonrandomized diagnostic accuracy studies with one or more important limitations causing serious concern about internal validity or external generalizability of the results.	Alternative options may be equally reasonable.
Insufficient	Evidence may be of such poor quality, conflicting, lacking (i.e., studies not done), or not externally generalizable to the target clinical population such that the estimate of the true effect of the test is uncertain and does not permit a reasonable conclusion to be made.	Insufficient evidence exists to recommend for or against routinely offering the diagnostic test.

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TABLE 3. ORGANIZATION OF THE TASK FORCE'S RECOMMENDATIONS

Location key	*Description*	*Page*
[I]	Introduction	-
[II]	Methods	-
[III]	Thyroid Function Testing and Pregnancy	-
[IV]	Iodine Status and Nutrition	-
[V]	Thyroid Auto-Antibodies & Pregnancy Complications	-
[VI]	The Impact of Thyroid Illness upon Infertility and Assisted Reproduction	-
[VII]	Hypothyroidism and Pregnancy	-
[VIII]	Thyrotoxicosis in Pregnancy	-
[IX]	Thyroid Nodules and Thyroid Cancer During Pregnancy	-
[X]	Fetal and Neonatal Considerations	-
[XI]	Thyroid Disease and Lactation	-
[XII]	Postpartum Thyroiditis	-
[XIII]	Screening for Thyroid Dysfunction Before or During Pregnancy	-
[XIV]	Future Research Directions	-
[XV]	Disclosure Statement	-
[XVI]	Acknowledgements	-

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TABLE 4. REFERENCE RANGES FOR TSH AND FT4 DURING EARLY PREGNANCY WORLDWIDE

Author, Country (reference) (analyzing method)	N	Gestation (week)	TSH in mU/L		FT4 in pmol/L (ng/dl)			Population characteristics		
			Median	2.5th-97.5th	Median	2.5th-97.5th	(Median, 2.5th-97.5th)	Iodine insufficiency	Mean BMI	Ethnicities (%)
Bestwick *et al.*, Italy (24) (AutoDELFIA)	5505	<16	1.07	0.04 - 3.19	9.3	7.4 - 12.2	(0.73, 0.58 - 0.95)	Moderate-Mild	[a]	NR
Bestwick *et al.*, UK (24) (Advia Centaur)	16,334	<16	1.11	0.06 - 3.50	13.9	10.9 - 17.9	(1.08, 0.85 - 1.40)	Moderate-Mild	[a]	NR
Bocos-Terraz *et al.*, Spain (264) (Architect)	481	<14	0.94	0.41- 2.63	13.9	10.8 – 17.8	(1.08, 0.84 - 1.38)	Mild	NR	White (93%)
Gilbert *et al.*, Australia (271)[b] (Architect)	1817	9-13	0.74	0.02 - 2.15	13.5	10.4 - 17.8	(1.05, 0.81 - 1.39)	Borderline	NR	Australian
Lambert-Messerlian *et al.*, USA (270)[c] (Immulite 2000)	8351	T1	1.00	0.12 - 3.37	14.2	10.4 – 17.8	(1.10, 0.81 - 1.38)	Mild	NR	White (67) and Hispanic (23)[d]
	8415	T2	1.19	0.35 - 3.35	13.0	9.3 – 16.2	(1.01, 0.72 - 1.26)			
Lazarus *et al.*, USA (139,265)[e]	2172	10-13	0.94	0.02 - 2.69	14.7	11.4 - 18.6	(1.15, 0.89 - 1.45)	Mild	NR	Hispanic (37), White (29), Black (27), Asian (8)
	2683	14-20	1.14	0.15 - 3.11	12.0	9.3 - 15.2	(0.94, 0.73 - 1.19)			
Li *et al.*, China (17) (Cobas Elesys 601)	640	7-12	1.47	0.10 - 4.34	15.8	12.3 - 20.9	(1.23, 0.96 - 1.63)	Proven sufficient[f]	NR	Chinese (presumed)
Männistö *et al.*, Finland (266) (Architect i2000)	4333	T1	1.11	0.08 – 3.54	15.3	11.7 – 22.8	(1.12, 0.86 - 1.58)	Sufficient	22.4	Finnish (presumed)
	747	T2	1.37	0.11 – 4.24	14.6	11.2 – 23.4	(1.13, 0.87 – 1.82)			
Medici *et al.*, the Netherlands (267) (Kryptos ECI)	5186	8-18	1.30	0.03 - 4.04	14.7	10.4 - 22.0	(1.15, 0.81 - 1.72)	Proven sufficient[f]	24.5	Dutch (52), Surinamese/Antillean (12), Turkish (8), Moroccan (6)
Pearce *et al.*, USA (142) (Advia Centaur)	585	<14	1.1	0.04 - 3.60	2.1[h]	1.5 - 2.9[g]	-	Borderline	NR	White (77) and Black (10)
Quinn *et al.*, Russia (272) (Abbott AxSYM)	380	T1	1.66	0.09- 4.67	-	-	-	Moderate	NR	Russian (presumed)
	549	T2	2.00	0.20- 4.68	-	-	-			
Springer *et al.*, Czech Republic (268) (ADVIA Centaur)	4337	9-11	1.21	0.06 - 3.67	-	-	-	Mild	NR	Caucasian (99)
Stricker *et al.*, Switserland (262) (Architect i2000SR)	575	6-12	0.95	0.07 - 2.82	13.9	10.5 - 18.5	(1.08, 0.82 - 1.44)	Sufficient	NR	Swiss (presumed)
	528	T2	1.02	0.20 - 2.79	12.2	9.5 - 15.7	(0.95, 0.74 - 1.22)			

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Vaidya *et al.*, UK (Modular E 170) (2012) [18]	1089	<12	1.08	0.14 - 3.19	14.6	10.7 - 19.4	(1.12, 0.83 - 1.59)	Mild-moderate	NR	White (91) and South Asian (4)

Studies were selected according to the following criteria: N≥500, exclusion of TPOAb positive women and availability of data from the manuscript or via personal communication. Iodine status was estimated based on references from article, WHO iodine status reports or from the Vitamin and Mineral Nutrition Information System (VMNIS).

TSH, thyroid-stimulating hormone; FT4, free thyroxine; NR, Not reported; T1, first trimester; T2, second trimester.

[a] Weight reported (Bestwick *et al.* median weight 59 kg in Italian and 67 kg in UK population); [b] Reported FT4 level is a mean; [c] Limits are 5th and 98th percentiles for TSH and 2nd and 95th percentiles for FT4; [d] Based on reports of the total FASTER population; [e] FT4 determined in normal-range TSH only; [f] Based on iodine measurements in study population; [g] Free T4 index (reference range 1.0-4.0); [h] High hCG levels excluded.

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TABLE 5. STUDIES INVESTIGATING SUBCLINICAL HYPOTHYROIDISM & ADVERSE MATERNAL OUTCOMES

	Population selection	TFTs	Definition of SCH (TSH value in mU/L)	Outcome	Adjusted analysis	Finding:	Comments
Casey et al. N=17,298, (261)	Non-selected, population-based	<20 wks	TSH >97.5th % (2.74-5.09 mU/L; gest. age specific)	Perinatal outcomes	No	* Preterm delivery: Unadjusted RR 1.8 [1.1-2.9] * Abruption: Unadjusted RR 3.3 [1.1-8.2]	
Cleary-Goldman et al. N=10,990 (289)	Non-selected, population-based	1st & 2nd trimester (two measurements)	TSH > 97.5th % (1st 4.28 mU/L; 2nd 3.93 mU/L)	Perinatal outcomes	Yes	No association	
Benhadi et al. N=2497 (287)	Non-selected, population-based	Mean 13 wks, up to end 2nd trimester	TSH >5.6 mU/L	Pregnancy loss	Yes	OR 1.8 [1,07-3,03] per TSH doubling	Small number of subjects in the high TSH cohort.
Mannisto et al. N=5805 (295)	Non-selected, population-based	Mean 10 wks, <20wks	TSH > 95th % (3.6 mU/L)	Perinatal outcomes	No	No association	* Analysis of only 5808 out of 9247 subjects. * TPOAb and TGAb assoc with perinatal mortality, after adjustment for age &parity TPOAB RR 3.2 [1.5-7.1]
Negro et al. N=4123 (286)	Non-selected, population-based	<11 weeks	TSH 2.5-5.0 mU/L	Pregnancy loss Preterm delivery	No multivariate analysis; Adjusted only for smoking	* Pregnancy loss OR 1.16/mIU [1.00-1.34] * Preterm delivery - no association	Study inclusive of only TPO-ab negative women
Mannisto T et al.	Non-selected,	Mean 11 weeks	TSH > 95th %	Pregnancy complications	Yes	No association	Study primarily focused on endpoints

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N=5,805 (294)	population-based		(3.6 mU/L)				of preeclampsia & gestational diabetes
Sahu et al. N=633 (279)	Non-selected, population-based	13-26 weeks	TSH > 5.5 mU/L (not pregnancy adjusted)	Pregnancy and perinatal complications	No	Cesarean section rate for fetal distress: OR 2,8 [1,2-6,6] (P=0.04)	
Su et al. N=1017 (291)	Non-selected, population-based	Until 20 weeks	TSH > 95% (3.77-4.35 mU/L; gest. age specific)	Pregnancy, perinatal & child development outcomes	Yes	* fetal distress: OR 3.65 [1.44 –9.26] * preterm delivery: OR 3.32 [1.22–9.05], * poor vision development OR 5.34 [1.09 –26.16] * neurodevelopmental delay OR 10.49 [1.01–119.19]	* No data on TPOAb status. * small numbers of affected individuals leading to low power for statistical analysis.
Karakosta et al. N=1170 (292)	Non-selected, population-based.	Mean 14 weeks	TSH > 97.5%, Trimester specific (1^{st} >2.53 mU/L; 2^{nd} >2.73 mU/L)	GDM and perinatal outcomes	Yes	* Low birth wt, RR 3.1[1.2-8] * Gestational Diabetes Mellitus (only if TPOAb+), RR 4.3 [2.1-8.9]	
Lazarus et al. N=21,846 (306)	Non-selected, population-based	Median 12 weeks	TSH >97.5% Variable in time (UK >3.65 mU/L; Italy >3.50 mU/L)	Child IQ	N/A	No association	
Korevaar et al. N=5971 (19)	Non-selected, population-based	Mean 13.2 weeks	TSH > 97.5% (>4.04 mU/L)	Premature delivery	Yes	OR 1.87 (1.11-1.34)	Not significant finding after exclusion of TPO-Ab positive subjects
Ong et al. N= 2411	Selected population of women attending private clinic for	Mean 11.1 weeks	TSH>97.5%, (TSH >2.15 mU/L)	Pregnancy & Fetal Outcomes	Yes	No association	

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(280)	screening						
Chen et al. **N= 8012** **(281)**	Non-selected, population-based	14% 1st trimester, 33% 2nd trimester, 53% i 3rd trimester	TSH > 97.5% (1st >3.47 mU/L; 2nd >3.81 mU/L; 3rd >4.99 mU/L)	Hypertension, PROM, low birth weight, IUGR	Yes	Hypertension: OR 2.24 [1.25-4.02], PROM: 6.01 [3,98-9,10], IUGR 3,34 [1,75-6,38], and LBW 2,92 [1,65-5,16]	majority of subjects assessed late in pregnancy (3rd trimester)
Godoy et al. **N= 5646** **(282)**	Non-selected, population-based	Median 13.2 weeks	TSH > 97.5% (TSH >4.04 mU/L)	Childhood growth, body composition & cardiovascular characteristics.	Yes	No association	
Medici et al. **N=5153** **(285)**	Non-selected, population-based	13.5 weeks	TSH > 97.5% (TSH >4.04 mU/L)	Blood pressure and hypertensive disorders	Yes	No association	
Liu et al. **N=3147** **(288)**	Selected healthy population, population-based	4-8 weeks	TSH > 97.5% (TSH 5.22)	Miscarriage	Yes	Increased risk for women when TSH > 5.22 (OR 3.4 (1.6-7.2)), or women with thyroid autoimmunity (OR 2.7 (1.4-5.1)). Synergistic worsening when both SCH and autoimmunity together.	Thyroid autoimmunity defined as either TPOAb or TgAb positivity.
Leon et al. **N=2170** **(283)**	Non-selected, population-based	Mean 13.5 weeks	TSH > 95% (TSH >3.5 mU/L)	Pregnancy & Fetal Outcomes	Yes	No association	No analysis of sub-clinical Hypothyroidism
Kumru et al. **N= 497** **(293)**	Selected, healthy population; population-based	10-12 weeks	TSH > 95% (TSH level not reported)	Pregnancy and perinatal outcomes	Yes	Preterm delivery: OR 4,8 [1,89-12,42] No association with other maternal or perinatal outcomes.	* synergistic effect of thyroid hormone status and TPO Ab status analyzed.

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Pakkila et al. **N=5131** **(284)**	Non-selected, population-based	Mean 10.5 weeks	TSH > 3.1 mU/L in 1st or > 3.5 mU/L in 2nd	Attention-deficit Hyperactivity Disorder (ADHD)	Yes	*SCH was not associated with an increase in ADHD symptoms *TSH was continuously associated with ADHD symptoms in girls
Taylor et al. **N=769** **(318)**	Women prescribed levothyroxine , population-based	1st trimester	3 endpoints: >2.5 mU/L , >4.5 mU/L , >10 mU/L	Miscarriage	Partial	*TSH >4.5 associated with an increased risk of miscarriage. Graded effect with increasing TSH

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TABLE 6. TPO-ANTIBODY POSITIVITY & ADVERSE MATERNAL OUTCOMES

	Population selection	TFTs	Outcome	Adjusted analysis	Association with antibodies	Additive effects SCH	Comments
Cleary-Goldman et al. **N=10,990 (289)**	Non-selected, population-based	1st & 2nd trimester (two measurements)	Perinatal outcomes	Yes	TPOAb positivity associated with premature rupture of membranes (OR 2.4-3.1)	Not investigated	
Benhadi et al. **N=2497 (287)**	Non-selected, population-based	Mean 13wks, up to end of 2nd trimester	Pregnancy loss	Yes	TPOAb positivity not associated with miscarriage.		*Adjustment for TSH did not change significant continuous association for TSH. *Absolute risk very low
Mannisto et al. **N=5805 (295)**	Non-selected, population-based	Mean 10wks, up to 20wks	Perinatal outcomes	No	If TgAb positive, a larger proportion of noncephalic presentation at birth (3.6 vs 6.3%), as well as perinatal mortality (0.8 vs 1.2%) If TPOAb positive, larger proportion of LGA (5.0 vs 2.4%) and perinatal mortality (2.4 vs 0.8%)	Not investigated	
Karakosta et al. **N=1170 (192)**	Non-selected, population-based.	Mean 14 wks	GDM and perinatal outcomes	Yes	OR 1.7 for spontaneous preterm delivery.	TAI + TSH >97.5%: OR 4.3 for GDM TAI + TSH >97.5%: OR 3.1-3.7 for LBW	Thyroid autoimmunity defined as positive TPOAb and/or TgAb

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Korevaar et al. **N=5971 (219)**	Non-selected, population-based	Mean 13.2 weeks	Premature delivery	Yes	TPO pos. + TSH >97.5%: OR 2.53* TPO pos. + TSH >2.5 mU/L: OR 2.18* TPO pos.+ TSH >2mU/L: OR 1.75 (ns)* TPO pos. + TSH>median: OR 1.4 (ns)*		
Medici et al. **N=5153**	Non-selected, population-based	13.5 weeks	Blood pressure and hypertensive disorders	Yes	No association for TPOAb pos.		
Liu et al. **N=3147 (288)**	Selected healthy population, population-based	4-8 weeks	Miscarriage	Yes	Thyroid Autoimmunity alone OR 2.71 TAI with TSH 2.5-5.22: OR 4.96 TAI with TSH >5.22: OR 9.56		TAI defined as positive TPOAb and/or TgAb with normal TSH and fT4
Päkkila et al. **N=5131 (284)**	Non-selected, population-based	Mean 10.5 weeks	ADHD symptoms	Yes	TPOAb positivity not associated with ADHD symptoms	Not investigated	Exclusion of TPOAb positive women did not change the results

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TABLE 7. HYPOTHYROXINEMIA & ADVERSE OBSTETRICAL AND NEONATAL OUTCOMES [a]

	Population selection	TFTs	Definition of hypothyroxinemia	Outcome	Adjusted analysis	Main result	Comments
				Obstetrical outcomes			
Korevaar et al. N=5971 (219)	Non-selected, population-based	<18wks	TSH 2.5-97.5th perc. & FT4 <2.5th perc.	Premature delivery	Yes	Hypothyroxinemia was associated with *A 2.5-fold increased risk of premature delivery and a 3.6-fold increased risk of very premature delivery, for spontaneous premature delivery this was 3.4 and 4.2-fold, respectively.	Hypothyroxinemia also associated with the risk of premature rupture of membranes (2.4-fold increased risk), also in spontaneous deliveries (2.7-fold increased risk).
Medici et al. N=5153	Non-selected, population-based	<18wks	TSH 2.5-97.5th perc. & FT4 < 2.5th perc.	Blood pressure and hypertensive disorders	Yes	No association	* Hyperthyroidism and high normal FT4 were associated with hypertensive disorders
Leon *et al.* N=2170 (283)	Non-selected, population-based	<24wks	TSH 5-95th perc. & FT4<5th perc.	Birth weight	Yes	*Hypothyroxinemia was associated with higher mean birth weight. *FT4 was negatively associated with birth weight.	
				Neurocognitive outcomes*			
Henrichs et al. N=3659 (297)	Non-selected, population-based	<18 wks	TSH <2.5mU/L with FT4 <10th perc. (mild) or FT4 <5th perc. (severe)	Language delay (18 and 30 months) and non-verbal cognitive delay (30 months)	Yes	*A 1.4 to 1.8-fold increased risk of expressive language delay (mild and severe hypothyroxinemia respectively). *A 2-fold increased risk of non-verbal cognitive delay (severe hypothyroxinemia)	Outcomes of delay defined as <15th age and sex specific percentile.
Craig et al. N=5560 (298)	Selected, population-based, nested case-control study	Mean 17.3 and 16.8 weeks (cases and controls)	FT4<3rd percentile	Bayley Scale Scores at 2 years	Yes	*Hypothyroxinemia was not associated with a lower score on cognitive, language or motor development domain.	After final selection, this study only had very low statistical power to detect a difference. Also the matching was suboptimal.

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Roman et al. N=4039 (299)	Non-selected, population-based	<18wks	TSH >0.03 & <2.5 mU/L & FT4 <5th perc.	Combination of the Pervasive Development Subscale of the CBCL checklist and the Social Responsiveness Scale	Yes	Hypothyroxinemia was associated with a higher mean autistic symptoms score and a 2-fold higher risk of pervasive development problems	No association for mild hypothyroxinemia (<10th FT4 perc.) Results were more apparent in boys.
Finken et al. N=1765 (300)	Non-selected, population-based	<15wks	FT4<10th perc.	Computerized assessment utilizing Amsterdam Neuropsychological Tasks	Yes	*Hypothyroxinemia was associated with a 41 millisecond slower response speed. *FT4 was also negatively associated with reaction time.	Reaction time is associated with brain morphologic and neurocognitive outcomes.
Julvez et al. N=1761 (301)	Non-selected, population-based	<20wks	Gestational age standardized FT4 <10th perc.	Bayley Scale Scores at 14 months	Yes	*Hypothyroxinemia was associated with a 2.2 point lower mean IQ *<5th percentile showed a statistically borderline result of 3.4 point lower mean IQ.	Also an association for trend when the trend of <10th, <5th and <2.5th percentiles was investigated.
Chassabian et al. N=3727 (302)	Non-selected, population-based	<18wks	FT4 <5th perc.	Non-verbal IQ (median age 6)	Yes	Hypothyroxinemia was associated with a 4.3 point lower mean IQ as compared to the rest of the population.	Hypothyroxinemia was not associated with brain morphology (on MRI), later paper showed this was inadequately analyzed.
Gyllenberg et al. N=1010 (303)	Selected, population-based, nested case-control study	Mean 11.0 and 10.8 weeks (cases and controls)	TSH 5-95th perc. & FT4<10th perc.	Schizophrenia	Yes	*Hypothyroxinemia was 1.75-fold as likely to be present in cases as compared to controls (11.8% versus 8.6%, respectively).	Subclinical hyperthyroidism was 1.9-fold more likely to be present in cases versus controls.
Modesto et al. N=3873 (304)	Non-selected, population-based	<18wks	TSH 0.1-2.5mU/L & FT4<5th percentile	Conners' ParentRating Scale–Revised Short Form (median age 8).	Yes	*Hypothyroxinemia was associated with higher parent-reported ADHD scores.	
Korevaar *et al.* N=3839	Non-selected, population-based	<18wks	Various FT4 cut-offs	Non-verbal IQ (median age 6), grey matter and		*For FT4 <9th percentile an association as seen with lower mean offspring IQ. The	Similar effects for high FT4

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317)		cortex volume (MRI scans at median age 8)	peak was at FT4<5th percentile. *Low FT4 was associated with lower grey matter and lower cortex volume (N=646)

[a]Available prospective observational studies since 2010

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TABLE 8. ADVANTAGES AND DISADVANTAGES OF THERAPEUTIC OPTIONS FOR WOMEN WITH GRAVES' DISEASE SEEKING FUTURE PREGNANCY

Therapy	Advantages	Disadvantages
Antithyroid drugs	Effective treatment to euthyroid state within 1-2 months	Medication adverse effects (mild 5-8 %; severe 0.2 %)
	Often induces gradual remission of autoimmunity (decreasing antibody titers)	Birth defects associated with use during pregnancy (MMI 3-4%; PTU 2-3% though less severe)
	Easily discontinued or modified. Treatment easy to take. Relatively inexpensive	Relapse after drug withdrawal likely in 50-70%
Radioactive Iodine	Easy oral administration	Repeat therapy at times necessary
	Reduction in goiter size	Rising antibody titers following treatment may contribute to worsening orbitopathy or fetal risk
	Future relapse of hyperthyroidism very rare	Lifelong need of levothyroxine therapy following ablation
Thyroidectomy	Definitive therapy of hyperthyroidism. Stable euthyroid state easily achieved on replacement levothyroxine therapy	Life-long need for levothyroxine supplementation
	Post surgery, gradual remission of autoimmunity occurs	Surgical complications occur in 2-5%
	Goiter disappears	Healing and recovery from surgery. Permanent neck scar

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TABLE 9. ATA SONOGRAPHIC PATTERNS AND ESTIMATED RISK OF MALIGNANCY FOR THYROID NODULES
(ADAPTED FROM ATA 2015 GUIDELINES WITH PERMISSION)

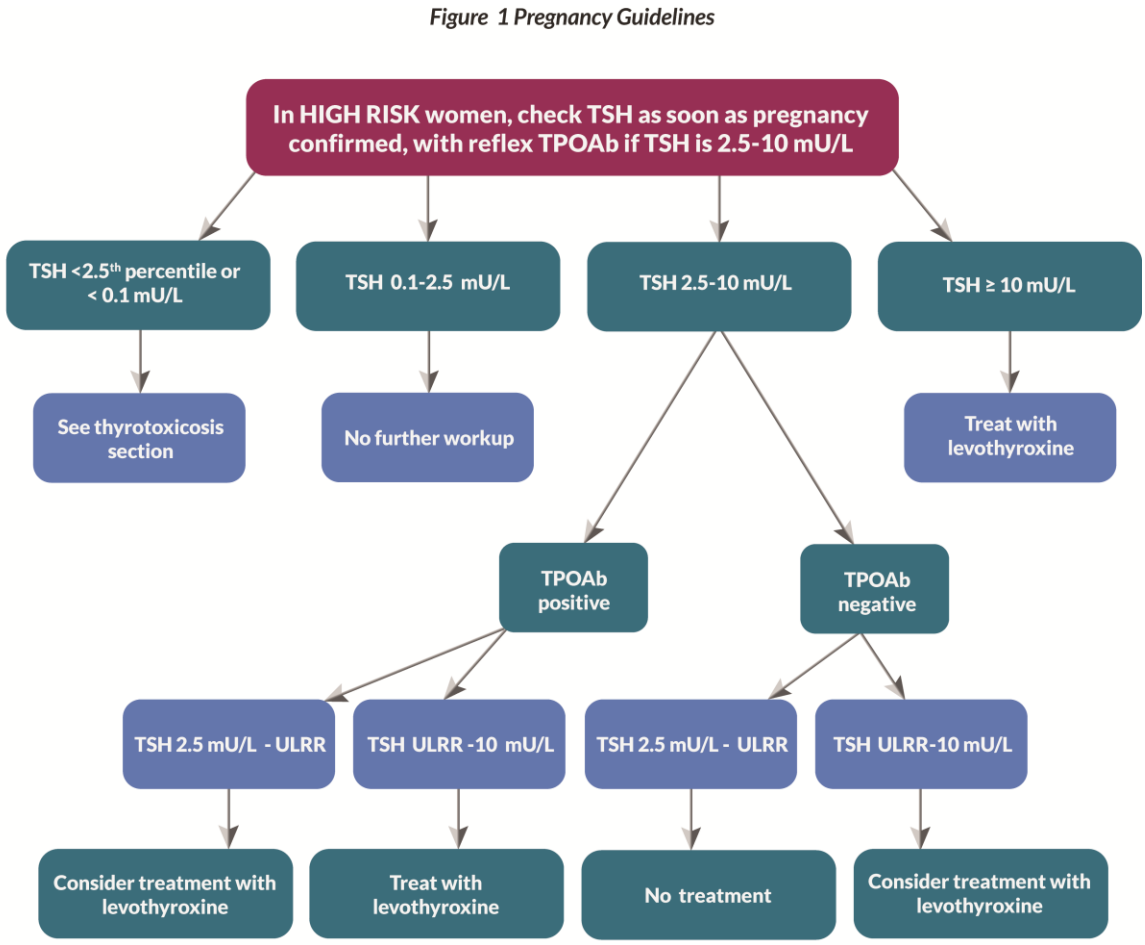
Sonographic Pattern	Ultrasound features	Estimated risk of malignancy	FNA Size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule ***with*** one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	>70-90%	Recommend at > 1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins ***without*** microcalcifications, extrathyroidal extension, or taller than wide shape	10-20%	Recommend at > 1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, ***without*** microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	5-10%	Recommend at > 1.5 cm
Very low suspicion	Spongiform or partially cystic nodules ***without*** any of the sonographic features described in low, intermediate or high suspicion patterns	< 3%	Consider at > 2 cm Observation without FNA is also a reasonable option
Benign	Purely cystic nodules (no solid component)	< 1%	No biopsy

Ultrasound-guided FNA is recommended for lateral neck cervical lymph nodes that are sonographically suspicious for thyroid cancer

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FIGURE 1. TESTING FOR THYROID DYSFUNCTION IN PREGNANCY



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