

American Thyroid Association 2026 Guidelines for Thyroid Disease in Preconception, Pregnancy, and Postpartum

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Background: Thyroid disease in pregnancy, preconception, and postpartum is a common and clinically relevant problem. Since the publication of the American Thyroid Association (ATA) guidelines in 2017, substantial new clinical and scientific evidence has become available. The aim of these guidelines is to provide clinicians, patients, researchers, and policymakers with evidence-based recommendations on the care of women with thyroid disease before, during, and after pregnancy.

Methods: The clinical questions addressed were informed by prior ATA guidelines, stakeholder feedback, a global needs assessment, and input from the multidisciplinary task force. Systematic literature searches were conducted with the support from a medical librarian and evaluated using the Grading of Recommendations,

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Assessment, Development, and Evaluation framework. Recommendations were formulated based on the quality of evidence, balance of benefits and harms, patient values, feasibility, and equity. Where data were limited, Good Practice Statements were formulated. The task force included representatives from 10 international societies as well as patient advocacy groups and a methodologist.

Results: The updated guidelines include recommendations on thyroid function testing, iodine supplementation, thyroid autoimmunity, hypothyroidism, hypothyroxinemia, hyperthyroidism and Graves' disease, thyroid nodules and cancer, and postpartum thyroid dysfunction for women with infertility, pregnant women, and women during postpartum and/or lactation. Recommendations are presented using recommendation tables, additional practical considerations are highlighted in boxes, and background information is provided in the text, tables, and figures per disease entity and chronological subset.

Conclusions: These 2026 ATA guidelines provide updated, evidence-based recommendations for the diagnosis and management of thyroid disease in women during preconception, pregnancy, and postpartum. While acknowledging that much of the evidence remains of low-to-moderate quality, these guidelines represent current best practices and consensus among international experts from different fields, offering an optimized framework for individualized patient care.

Keywords: thyroid, preconception, pregnancy, postpartum, lactation, ATA pregnancy guidelines

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A. Introduction

This document is an update of the 2017 American Thyroid Association (ATA) guidelines for the diagnosis and management of thyroid disease during pregnancy and postpartum.¹ Since the release of the 2017 guidelines, substantial new data have improved our understanding of gestational thyroid physiology; definition of (ab)normal thyroid function tests; quantification of thyroid-disease-related risks; and the harms, benefits, and optimal timing of treatment options for thyroid conditions preconception, in pregnancy, and postpartum.

We established three main goals at the start of the process of updating the guidelines. The first goal was to improve the impact of the guidelines. To achieve this, we first formed key collaborations with 10 international societies, including those that represent obstetricians, fertility specialists, surgeons, and patients with thyroid disease. Representatives of these societies were then invited to serve as committee/writing group members to optimize the content and readability of the document among these disciplines. Second, we wanted to modernize the appearance of the guidelines. To achieve this goal, we intentionally avoided using the text of previous guidelines as a starting point, opting instead to depart from the traditional question-based outline that has generally characterized ATA guidelines since 2006.² We also had access to a professional graphic designer and, in our writing process, prioritized clinical pearls and data most relevant for clinicians, shortened recommendations, and included more flowcharts. Third, we wanted to strengthen the evidence-based approach of the guidelines. To achieve this goal, we followed a “blank canvas” approach in which we searched the full literature, not solely focusing on studies published since the previous guidelines, set up a framework of systematic literature searches with the help of a medical librarian, and worked in close consultation with an expert methodologist to adhere to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework. These modifications, combined with the results of new studies, form the basis for the changes in these updated guidelines as compared with their previous iteration.

With the exception of some subcategories, the quality of most evidence that supports the recommendations in this guideline remains low. Thus, besides the changes noted above, we now include the category of Good Practice Statements (GPSs) for recommendations that the writing committee deemed important but for which the lack of data does not allow for a formal certainty of evidence rating according to the GRADE framework. In addition, we also now highlight practical considerations for clinical management in separate figures and boxes. Finally, we communicate absolute rather than relative risks as much as possible.

These guidelines have been endorsed by:

- American Association of Clinical Endocrinology
- American College of Obstetricians and Gynecologists
- Asia and Oceania Thyroid Association
- Endocrine Society
- European Board and College of Obstetrics and Gynaecology
- European Society of Endocrinology
- European Society of Human Reproduction and Embryology
- European Thyroid Association
- International Association of Endocrine Surgeons

- Iodine Global Network
- Latin American Thyroid Society
- Thyroid Federation International

B. Methods

The guidelines writing group consisted of 20 individuals: 18 physician-scientists with thyroid expertise representing seven international societies, 1 physician-methodologist, and 1 patient representative. The committee members were selected for their established expertise in thyroidology spanning the life stages of preconception, pregnancy, and postpartum. Each member belonged to up to two out of a total of six working groups within the different chapters in this guideline (one working group for each of the Sections from C to I, with the exception of one combined working group for Sections D and H). The composition of the writing committee was also determined from multiple collateral relationships that the co-chairs and the ATA had developed with 10 international scientific societies representing key stakeholders in thyroidology, general endocrinology, obstetrics and gynecology, and reproductive endocrinology, from which representatives were invited to serve. The chairs of the guideline committee were Tim Korevaar and Angela Leung (ATA), with the ATA represented by Erik Alexander, Chrysoula Dosiou, Sun Lee, Spyridoula Maraka, Kara Meister, Lilah Morris-Wiseman, Caroline Nguyen, and Zhongyan Shan. The Latin American Thyroid Society was represented by Gabriela Brenta. The European Thyroid Association was represented by Sofie Bliddal. The Asia and Oceania Thyroid Association was represented by Haixia Guan. The Endocrine Society and the Iodine Global Network were represented by Elizabeth Pearce. The European Society of Endocrinology was represented by Kristien Boelaert. The American College of Obstetricians and Gynecologists was represented by Sarah Kilpatrick. The American Society for Reproductive Medicine was represented by Jennifer Eaton. The European Society of Human Reproduction and Embryology was represented by Rima Dhillon-Smith. Our patient representative and member of the Thyroid Federation International was Bente Julie Lasserre. Finally, these guidelines were also supported by Roger Chou, a methodologist.

Task force chairs were proposed by the ATA Board of Directors. Both Task Force Chairs and Members were selected for their expertise and evaluated for potential conflicts of interest (COI) by the ATA Guidelines and Statements Committee and the Board of Directors. Any potential financial competing interests were declared (see the Author Disclosure Statement), and, where appropriate, individuals were not involved in the final approval of recommendations for which a potential or perceived conflict was identified. Competing interests were re-evaluated annually by the Task Force chairs and members. The opinions expressed herein are those of the authors, and the Task Force had complete editorial independence from the ATA. Except for the methodology consultant (R.C.), who received consultant fees from ATA, no individual Task Force members received funding from the ATA or from industry for work on this statement.

To inform the key content of the guidelines, we distributed a needs assessment questionnaire to the ATA membership from February to March 2022, to solicit suggestions and affirm content deemed most timely to the research needs and current clinical practice of the field. Input was gathered from

a total of 388 respondents from across the globe (Europe 33%, North America 31%, Asia 25%, South America 8%, Africa/Australia both 1%), mostly attending physicians (48%), clinical practitioners (90%) (composed of 40% endocrinologists, 26% obstetricians/gynecologists, 24% reproductive medicine specialists, and the remainder as primary care clinicians, surgeons, etc.). The respondents provided 15 proposed topics and 11 main outcomes of interest that were used to inform the overall outline of the guidelines, organized as 122 PICO (population, intervention, control, outcome) questions with corresponding inclusion and exclusion criteria for the selection of relevant literature. For each of the six working groups (topics represented by Sections C–I), we identified a set of the most clinically relevant outcomes utilizing input from the needs assessment questionnaire and priority voting by the working group members. We subsequently performed a series of systematic literature reviews together with the Erasmus University Medical Center Medical Library (Elise Krabbendam, Biomedical Information Specialist) in consultation with the committee's methodologist (Roger Chou, MD; see supplemental material). We first performed an overarching systematic literature review (April 12, 2022, and again on February 1, 2024) that included all predefined exposures and outcomes mentioned in the PICO questions, with the aim of identifying randomized trials and meta-analyses only. We then selected the one to four most important PICO questions for each working group (based on group consensus) for a question-specific systematic literature review with the aim of identifying any relevant literature regardless of study type. Literature for the remaining questions was identified through individual literature searches following an online PubMed training course. The results of the included studies were then entered into a data extraction table that also included quality rating metrics (Supplementary Table S1). During the time between systematic literature searches and submission to the journal, additional relevant studies were added per the insights of the committee. For all systematic literature search outputs, studies eligible for inclusion were independently assessed for suitability by two committee members (title and abstract screening, full-text screening, and quality assessment for overarching search), and any disagreements were resolved by discussion with a co-chair (Supplementary Table S2). The publication process consisted of reviews by, and comments from, the ATA Guidelines and Statements Committee, ATA Board of Directors, the ATA membership at large, and the membership of endorsing societies before the article was submitted to *Thyroid* which then underwent peer review.

The methods and output were based on guidance provided in the GRADE series.^{1,2} After defining the key clinical questions and performing corresponding systematic literature searches to identify relevant literature, we created an overview of (average) effects on relevant outcomes and rated the quality of the evidence for each. The quality (certainty) of the evidence supporting each recommendation was classified as very low, low, moderate, or high using the GRADE approach, based on study design (randomized trials or non-randomized studies) and the GRADE domains (limitations/risk of bias, inconsistency, imprecision, indirectness, and publication or reporting bias). The strength of each recommendation was defined as strong (text worded as “should”) or conditional (text worded as “may”) and was based on the quality of the evidence, the balance of desirable and undesirable outcomes, potential impact of individual values and

preferences on decisions, and other factors (acceptability, feasibility, cost/resources, and equity). The meaning of a strong recommendation is that all reasonably informed persons (clinicians, policymakers, and patients) would desire the management in accordance with the recommendation. For a conditional recommendation, most persons would still act in accordance with the guideline, but a substantial number would not, for example, conditional on patient preferences. Where applicable, this is expanded upon in the general text. An alternative to graded recommendations was GPSs, which were reserved for situations for which direct evidence on benefits and harms was unavailable or lacking, but there was high certainty of benefit based on indirect evidence, and there was consensus that not following the GPS would be inconsistent with the standard of care. Operationally, a GPS is similar to a strong recommendation (i.e., should be followed in all or almost all situations).³ Consensus was sought for all recommendations and reached unanimously for the vast majority of recommendations.⁴ For the exceptions, we followed an informal consensus process as based on a predefined 75% approval rate from the committee members who were ATA members, with all dissensions summarized in Supplementary Table S3. It should be noted that the recommendations are general guidance and should be adapted for each individual patient scenario, based on local resources/expertise and shared decision-making between the patient, clinician, and other health care team members.

C. Thyroid Physiology and Thyroid Function Testing

Thyroid function tests are among the most frequently ordered laboratory tests in otherwise healthy women of reproductive age.^{5–7} Specifically for women planning pregnancy, pregnant women, or those who are postpartum, there is generally a lower threshold to perform thyroid function testing. This is partly because, during these specific life phases, normal symptomatology can overlap with that of thyroid disease, while simultaneously, there is a peak in the prevalence of common thyroid disorders (such as Graves' disease and thyroiditis). Furthermore, most health care practitioners are aware that overt thyroid disease is associated with adverse fertility and pregnancy outcomes. Due to an increased testing frequency, mild thyroid function test abnormalities are commonly identified in women of reproductive age. It remains difficult to distinguish whether these represent early-stage thyroid disease or nonpathogenic thyroid function test abnormalities, especially because of changes in thyroid physiology and an increase in analytical variations around ovarian stimulation in assisted reproductive technology (ART), pregnancy, and postpartum. Therefore, thyroid function testing strategies and interpretation preconception, in pregnancy, and the postpartum period should anticipate the physiological and analytical alterations of thyroid function parameters to optimize clinical care.

What is new in this guideline: (1) We now discuss multiple testing options for the identification of (ab)normal thyroid hormone availability during pregnancy and outline advantages and disadvantages of alternative testing methods that impact laboratory and trimester-specific free thyroxine (fT4) reference intervals. (2) We provide an update on risk factors for thyroid disease during pregnancy that can be used to support an indication for thyroid function testing during pregnancy, removed risk factors that had only limited potential to differentiate outcomes (e.g., parity, maternal age, and

body mass index [BMI]), and updated the definitions of the remaining previously used risk factors.

Thyroid physiology before, during, and after pregnancy

Thyroid parameters are not meaningfully impacted during a normal menstrual cycle. During ovarian stimulation for

fertility treatment, the increase in estrogens causes an increase in type 3 deiodinase activity and thyroxine (T₄)-binding globulin (TBG) concentrations which necessitates increased thyroid hormone production and causes a slight rise in thyrotropin (TSH) concentrations (Fig. 1A).^{8–11} Pregnancy itself is also associated with changes in thyroid

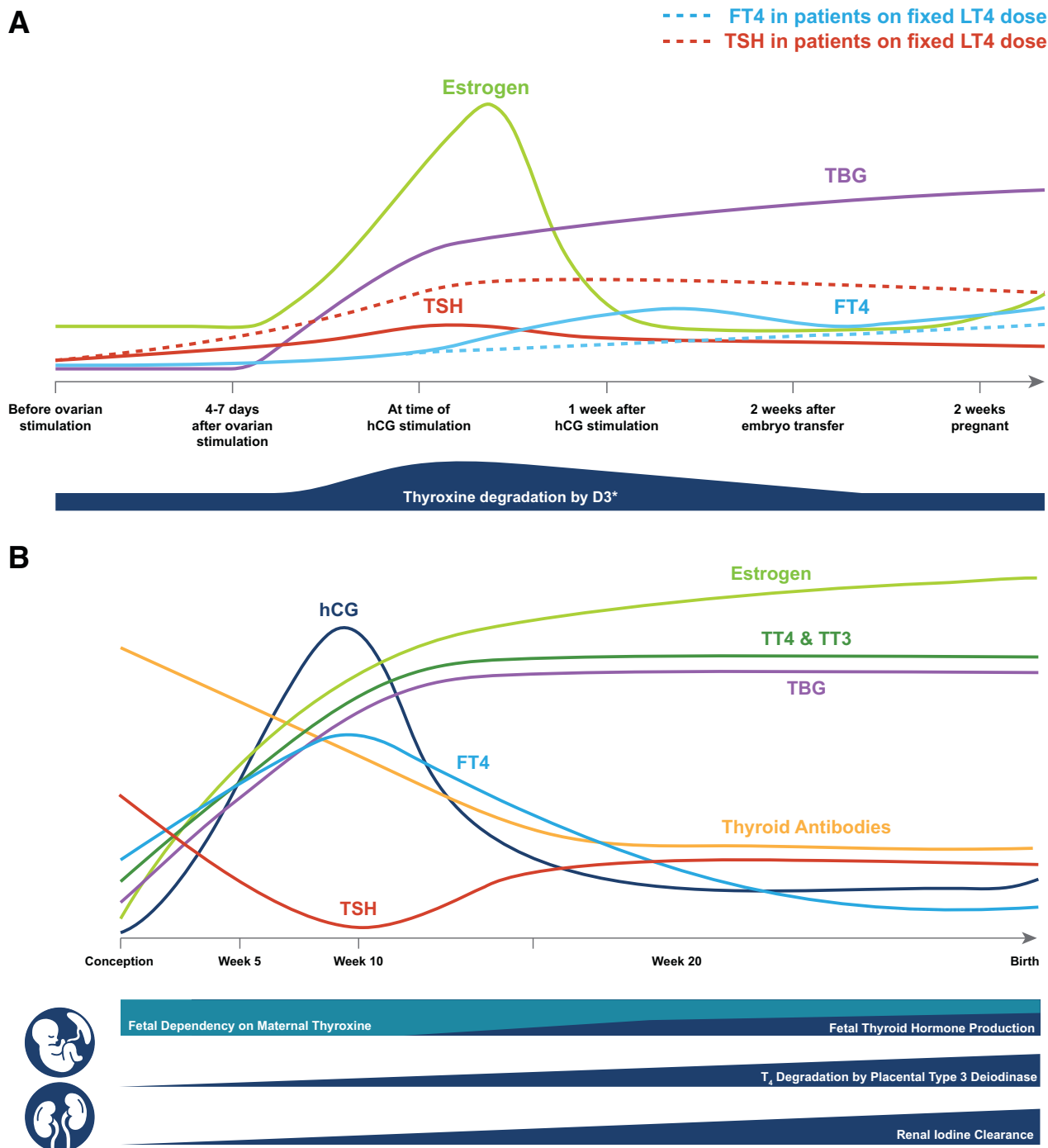


FIG. 1. (A) Thyroid physiology during ovarian stimulation. Physiological alterations of serum TSH, fT₄, and TBG concentrations are expected from the rise of estrogen during ovarian stimulation. Thyroxine requirements are extracted from studies of women with hypothyroidism taking fixed levothyroxine doses. (B) Thyroid physiology during pregnancy. Physiological alterations of serum TSH, TT₃, TT₄, fT₄, and thyroid antibody concentrations are expected from the effects of hCG, estrogen, and other factors during pregnancy. TT₃, total triiodothyronine; TT₄, total thyroxine; TBG, thyroxine-binding globulin; hCG, human chorionic gonadotropin; TSH, thyrotropin; fT₄, free thyroxine; TBG, thyroxine-binding globulin.

physiology that make the interpretation of thyroid function tests different in pregnant compared with nonpregnant individuals (Fig. 1B). For example, TBG increases from week 7 of gestation to reach a peak by approximately week 16 and stabilizes thereafter,¹² and logically, total thyroid hormone concentrations (T4 and triiodothyronine [T3]) follow this same pattern. As pregnancy progresses, there is an increase in the transfer of maternal T4 to the fetal compartment, an increase in T4 degradation by type 3 deiodinase expressed in the placenta, and an increase in renal iodine excretion. Furthermore, through its affinity for the TSH receptor, human chorionic gonadotropin (hCG) stimulates thyroid hormone production with peak stimulatory effects around the end of the first trimester.¹⁰ The healthy thyroid system adapts to these alterations through changes in thyroid hormone production, iodine uptake, and regulation of the hypothalamic–pituitary–thyroid axis.^{8–10} The net effect of all physiological changes is a slight transient increase in fT4 and a decrease in TSH that is most pronounced at the end of the first trimester. Thus, in normal physiology, a TSH below 0.4 mU/L occurs frequently.^{13,14} Furthermore, the immune tolerance of pregnancy, necessary to tolerate the allogeneic fetus, is associated with a decrease in thyroid antibody concentrations as gestation progresses. This explains why Graves' disease can become quiescent during pregnancy and why thyroperoxidase antibody (TPOAb) positivity is less common in the third trimester than preconception.¹⁵ Nevertheless, from 28 weeks onward, there is a considerable increase in active transplacental IgG transport, and cord blood concentrations can ultimately increase to those of the mother.^{16–18} The subsequent immune system rebound that occurs postpartum is a precipitating factor for postpartum thyroiditis (PPT) and *de novo* or relapsed Graves' disease.¹⁵

In specific subgroups, physiological processes may have a different effect on clinical parameters. For example, in women with hypothyroidism using levothyroxine (LT4) and who are undergoing ovarian stimulation, the increase in TBG caused by high estrogen concentrations can cause a clinically relevant increase in TSH (mean: +1.50 mU/L) that persists into pregnancy and may necessitate an earlier or larger LT4 dose increase as compared with women with hypothyroidism who conceive naturally.¹⁹ Another example is twin pregnancies, in which there is a higher hCG concentration as compared with singleton pregnancies, causing a greater stimulation of thyroid hormone production, resulting in lower TSH and higher fT4 concentrations.^{20,21} Yet, for a twin pregnancy in a hypothyroid woman using LT4 (in which no or very little thyroïdal response to hCG stimulation can be anticipated), LT4 consumptive factors have a larger impact on thyroid physiology (i.e., larger volume expansion, larger fetal T4 transfer, higher type 3 deiodinase activity due to higher estradiol and a larger placenta) which could necessitate a larger LT4 dose increase as compared with a singleton pregnancy. A final example is TPOAb-positive women, who are known to have a slightly higher mean TSH and a higher risk of overt hypothyroidism, partly because of an impaired thyroïdal response to hCG stimulation during early pregnancy.^{22–25}

Knowledge regarding placental transfer of thyroïdal factors is key to understanding normal physiology and pathophysiology, as well as the risks and benefits of various

treatment modalities. As shown in Figure 2, thyroid hormones, thyroid antibodies, iodine, and antithyroid drugs (ATDs) all traverse the placental barrier.

Analytical considerations

Pregnancy-specific physiology can also affect thyroid function assay performance, a basic understanding of which is beneficial to health care practitioners. In addition to the aforementioned physiological changes, other changes, such as an increase in free fatty acids and a decrease in albumin concentrations,^{26–28} may influence the performance of fT4 immunoassays. It is known that these could result in falsely lower serum fT4 concentrations in a method-specific manner, especially during the second half of pregnancy.^{13,29–31} Recent data have renewed the favorability of the use of fT4 measurements analyzed via analog immunological methods early in pregnancy as compared with alternative options. Most notably, fT4 measured via analog methodology better correlates with TSH in the first trimester than total T4,³² and fT4 has also been associated with maternal and child outcomes, a finding which has not been demonstrated for other test methodologies.^{32–35} These findings suggest fT4 analog measurement is an appropriate marker of thyroid function in the first half of pregnancy.³⁶ The use of a laboratory and trimester-specific fT4 reference interval would likely eliminate any pregnancy-specific analytical changes³⁷ and is thus the preferred method for fT4 interpretation during pregnancy. However, such reference intervals cannot be effectively transferred amongst differing manufacturers or testing platforms and may not be widely available.

When pregnancy and trimester-specific reference intervals for fT4 are unavailable, alternative strategies for interpreting or assessing thyroid hormone availability during pregnancy can be considered, taking into account the advantages and disadvantages of each strategy. One option would be to use nonpregnancy reference intervals for fT4, taking into account that this will likely lead to small differences in diagnosis, including more diagnoses of overt hypothyroidism and isolated hypothyroxinemia, especially after the first trimester.³⁸ Another option is to use direct methods for measurement of fT4, such as equilibrium dialysis or ultrafiltration combined with liquid chromatography/tandem mass spectrometry. However, direct methods are not free from technical problems and are significantly more laborious, time-consuming, expensive, and less widely available. Comparisons of direct methods with commonly used immunoassays have yielded heterogeneous results.^{30,37,39,40} Another option is to use the fT4 index, which is defined as the total T4 adjusted for protein binding using the thyroid hormone binding ratio.⁴¹ This formula assesses whether the amount of total T4 present in serum can be accounted for by the amount of binding protein present. The fT4 index has limited availability, and gestational reference intervals are typically not established. Furthermore, the calculations may be insensitive to the dynamic changes of gestational thyroid function.⁴¹ Another option that could be considered is to use the total T4, adjusting for the increase expected by the TBG rise. Considering the changes of serum total T4 through pregnancy, the reference interval for total T4 can be adjusted by increasing the nonpregnant reference limits by 5% per week, beginning with week 7,

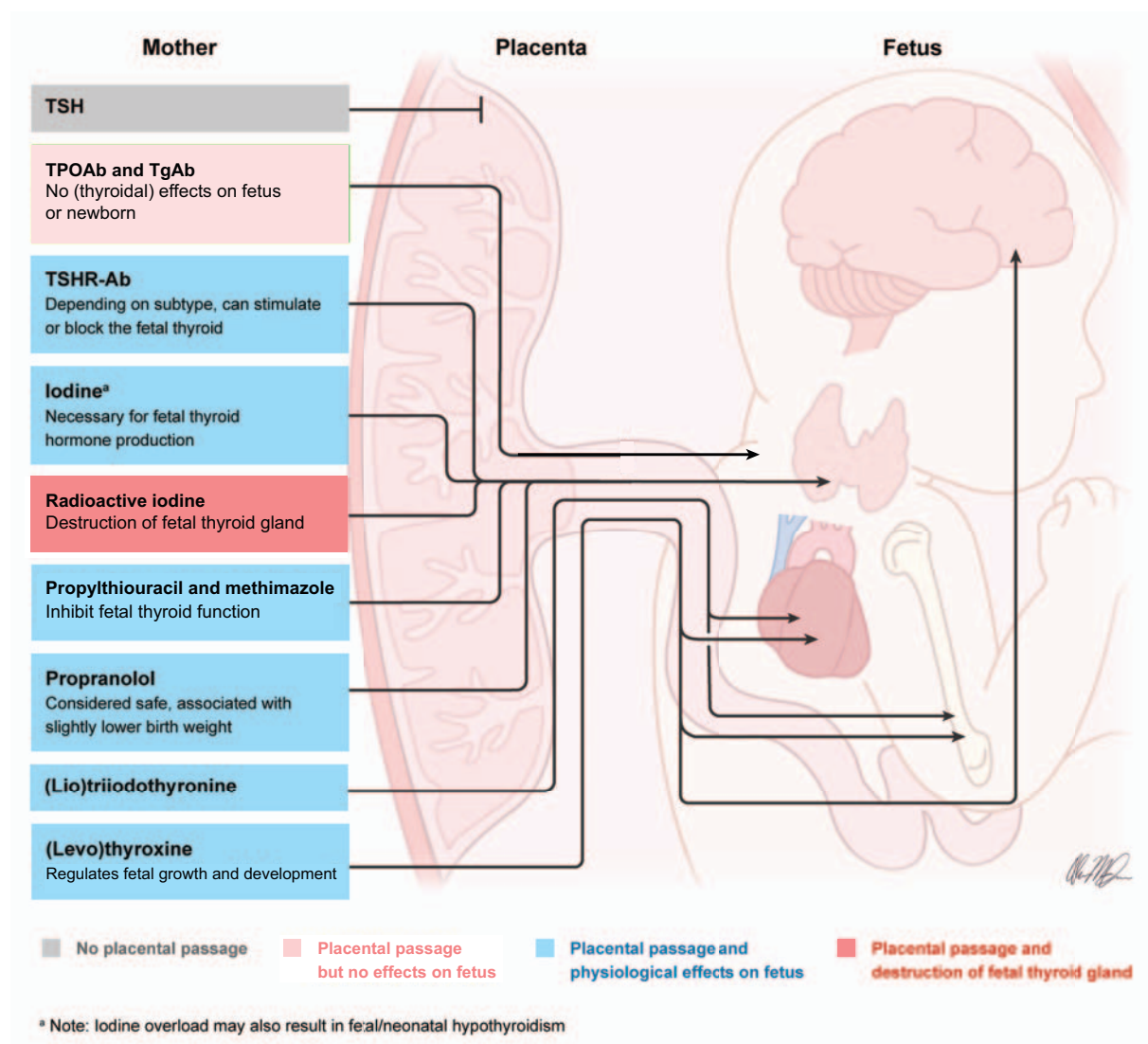


FIG. 2. Transplacental passage of thyroid parameters and drugs. Maternal TSHR-Ab, iodine, radioactive iodine, the antithyroid drugs (propylthiouracil and methimazole), propranolol, and the thyroid hormones [(l)io)thyronine and (levo)thyroxine] all traverse the placenta and have the potential to induce direct effects to the fetus. Maternal TPOAb and TgAb can also traverse the placenta but do not affect the fetus. Maternal TSH does not cross the placenta. TPOAb, thyroperoxidase antibody; TgAb, thyroglobulin antibody; TSHR-Ab, thyrotropin receptor antibody.

and plateauing at a 50% increase from week 16 of pregnancy onward.¹²

Importantly, maternal TSH remains the best marker of maternal thyroid status during pregnancy. TSH measurement by third generation immunoassays is not affected by the pregnancy-associated binding protein changes. However, different immunoassays may give different TSH results as is well-established in nonpregnant populations.⁴² Therefore, when there is concern over the correct interpretation of fT4 concentrations, the TSH result should be prioritized during evaluation. The general principle that the intraindividual thyroid function test variation is smaller than that between individuals also applies in pregnancy.^{43,44} Therefore, it is optimal to use the same TSH and/or

fT4 assay, or an alternative described above, for follow-up over the course of pregnancy.

Except for the characterization of hyperthyroidism, the relevance of measuring serum free or total T3 in pregnancy is generally low, as there is no clear association between these biochemical markers and adverse pregnancy or child outcomes other than gestational diabetes mellitus.^{45–47} In addition, maternal free or total T3 concentrations may not reflect T3 status in the fetal brain.⁴⁸ When T3 estimates are needed, it is reasonable to apply the same considerations as described above for free and total T4 estimates for interpretation. Considerations for free and total T3 measurements in hyperthyroidism during pregnancy are discussed in Box 5.

Definition of (ab)normal thyroid function tests

Recommendations Table 1: Definitions of (Ab)normal Thyroid Function Tests		Strength*	Level #
Preconception and during fertility treatment			
Apply the same definition of (ab)normal thyroid function tests to women planning a pregnancy as those used for the general non-pregnant population.	Good Practice Statement		
Pregnancy			
A lab and trimester-specific reference interval ^a for TSH and FT4 is suggested as the preferred standard for use during pregnancy.	Conditional	Low	
If a lab and trimester-specific reference interval for TSH is unavailable, a TSH reference interval of 0.1-4.0 mU/L can be used during the first and second trimesters. ^b	Conditional	Low	
If a lab and trimester-specific reference interval for FT4 is unavailable, the following options may be used to define (ab)normal FT4, with the understanding of the limitations inherent to each testing platform: - A FT4 surrogate (TT4 adjusted for gestational week^c or the FT4 index^d) - The non-pregnancy FT4 reference interval^e	Conditional	Low	
The concept that serum TSH concentrations typically best reflects maternal thyroid function should be emphasized during clinical decision-making.	Good Practice Statement		
The same thyroid function test methods/assay should be used for individual patient follow-up over the course of pregnancy to reduce analytic variability.	Good Practice Statement		

^a See the text and box for the recommended methodology to define TSH and FT4 reference intervals.

^b See text for those centers where the non-pregnancy upper limit for TSH is above 4.5 mU/L. For the third trimester, the reference intervals for general non-pregnant population TSH concentrations will likely suffice.

^c The non-pregnancy reference interval limit for total T4 can be used before gestational week 6. For gestational weeks 7 to 16, non-pregnancy reference interval limits for total T4 can be increased by 5% per week (total T4 percentage increase in pregnancy = [gestational week – 6] x 0.05) with a maximum increase of 50% by the 16th week of pregnancy. For gestational weeks >16, a 50% increase of total T4 may be estimated.

^d Typically defined as: TT4 (mcg/ml) x T3 uptake (%) / 100 (pregnancy reference intervals typically not available)

^e The assay-related underestimation of FT4 concentrations during the second half of pregnancy should be taken into account, which can lead to slightly more diagnoses of isolated hypothyroxinemia and overt hypothyroidism as compared to a laboratory and trimester-specific reference interval.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TSH, thyroid stimulating hormone; FT4, free thyroxine; TT4, total thyroxine

Dissenting comments for Recommendations Table 1 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

For women planning pregnancy or those who are postpartum, thyroid dysfunction is defined according to local reference intervals for TSH and fT4 used for the general population. During pregnancy, physiological and analytical alterations can be accounted for through the use of laboratory and trimester-specific TSH and fT4 reference intervals. Recommendations on the definition of an abnormal TSH and fT4 in pregnancy (Box 1) should be used to guide clinical practice and cannot replace clinical evaluation, risk assessment, and patient involvement through shared decision-making. Gestational TSH and (f)T4 measurements should be interpreted with the understanding of the limitations inherent to each reference interval. There remain considerable intra-assay and intralaboratory differences in TSH and, especially, fT4 measurements, despite (local) standardization efforts.⁴⁹ Laboratory and trimester-specific reference intervals are a statistical estimation of normal variation within a population. These do not incorporate the risk of adverse outcomes but remain the preferred method until risk-based intervals become available. The committee acknowledges, however, the fact that trimester- and laboratory-specific reference intervals are currently unavailable in the majority of hospitals worldwide. In such cases, clinicians can be guided by the knowledge of the physiological changes that occur in

healthy pregnant women with a decrease in TSH, especially in the first trimester. The 2017 ATA guidelines, after reviewing the significant geographic and ethnic diversity of TSH concentrations in pregnancy, recommended the following TSH cutoffs in the absence of laboratory and trimester-specific TSH reference intervals: reduction of the lower reference range by 0.4 mU/L and the upper reference range by 0.5 mU/L in the first trimester, followed by a gradual return to the nonpregnant range in the subsequent trimesters. Based on expert opinion and an extrapolation of average values from reference interval studies, this committee agrees that this is acceptable and would correspond, for the typical patient, to a first-trimester reference interval of 0.1–4.0 mU/L.^{38,50} An upper limit of 4.0 mU/L is about 0.5 mU/L lower than the non-pregnancy upper TSH limit for most assays. It would be reasonable for centers where the nonpregnancy upper limit is well above 4.5 mU/L to deduct 0.5 mU/L from the upper TSH limit instead.^{38,50} Owing to the large interassay differences in absolute fT4 concentrations, recommendations for absolute fT4 reference intervals are not feasible, but considerations for different alternatives are discussed above.

The abovementioned alternative strategies (e.g., a fixed TSH upper limit of 4.0 mU/L or deducting 0.5 mU/L from the nonpregnancy upper limit) were proposed with the aim

Box 1. Preferred definitions of thyroid function test abnormalities during pregnancy

- A laboratory and trimester-specific reference interval is optimally defined as the 2.5th-97.5th percentile range of a population representative of a healthcare provider's patient population that only includes women without major thyroid interfering factors (e.g. TPOAb negative women with a singleton pregnancy, no known thyroid disease, and no [regional] severe iodine deficiency).
- Various other factors that may be associated with higher mean TSH and FT4 concentrations (e.g. comorbidities, assisted reproductive technology, or thyroglobulin antibody [TgAb] positivity) have not been shown to substantially change the reference interval limits for TSH or FT4 during pregnancy. However, removal of additional cases from a study population could impact the quality of the reference intervals by lowering the number of included individuals.⁵⁰ Thus, it does not seem necessary to use these additional exclusion criteria.
- Thyroid dysfunction during pregnancy is defined as follows:
 - **Overt primary hypothyroidism:** increased (>97.5th percentile) TSH concentration with a decreased (<2.5th percentile) FT4 concentration.
 - **Subclinical hypothyroidism:** increased TSH concentration with a normal (2.5th -97.5th percentile) FT4 concentration.
 - **Isolated maternal hypothyroxinemia:** decreased FT4 concentration with a normal TSH concentration.
 - **Overt hyperthyroidism:** decreased TSH concentration with elevated FT4 and/or (F)T3 concentration.
 - **Subclinical hyperthyroidism:** decreased TSH concentration with normal FT4 and (F)T3 concentration.

TPOAb, thyroperoxidase antibody; TSH, thyroid stimulating hormone; FT4, free thyroxine; TgAb, thyroglobulin antibody; FT3, free triiodothyronine

to approximate laboratory- and trimester-specific TSH reference intervals in pregnancy.¹ However, recent studies have shown that these alternatives tend to misclassify a substantial number of patients. For example, for overt hypothyroidism in the first trimester, use of a fixed TSH upper limit of 4.0 mU/L would identify 46.1% of all women with overt hypothyroidism but identify the remainder as either euthyroid (11.9%), subclinically hypothyroid (36.8%), or

TSH) of overt and subclinical hypothyroidism may be transient in approximately half of all cases.^{51,52} This may suggest that future disease definitions and/or treatment indications could be improved by accounting for the persistent of disease upon remeasurement.

Thyroid function testing indications

Recommendations Table 2: Indications for Thyroid Function Testing		Strength*	Level #
<i>Pregnancy</i>			
All newly pregnant women should undergo clinical evaluation and assessment for risk factors ^a for thyroid dysfunction in pregnancy.		Good Practice Statement	
In women without known thyroid disease, it is suggested that TSH testing be offered upon a positive pregnancy test to those at increased risk of thyroid dysfunction during pregnancy. ^a		Conditional	Moderate
In women treated with levothyroxine, TSH testing may be performed upon pregnancy confirmation, approximately every 4 weeks during the first half of pregnancy, at least once in the third trimester, and 4-6 weeks after any dose adjustment.		Conditional	Moderate
<i>Postpartum</i>			
Apply the same thyroid function testing indications to postpartum women as those for the general non-pregnant population. Specifically for women using levothyroxine, thyroid function testing should be performed around 6 weeks postpartum or following any levothyroxine dose adjustment.		Good Practice Statement	

For recommendations preconception (including fertility treatments), see section E

^a As defined in Table 1

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TSH, thyroid stimulating hormone

Dissenting comments for Recommendations Table 2 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

with isolated hypothyroxinemia (5.2%), as compared with a laboratory with trimester-specific reference intervals.³⁸ However, it is still uncertain if this misclassification will cause clinical harm. These numbers are similar when the subtraction approach is used (46.1%, 13.5%, 35.2% and 5.2%, respectively).³⁸ Furthermore, recent data on the natural course of thyroid function test abnormalities during pregnancy suggest that mild cases (slightly increased

Thyroid function tests are some of the most frequently ordered laboratory tests. In women without known thyroid disease, infertility, or recurrent miscarriage, the indications for thyroid function testing for those planning pregnancy or those who are postpartum are similar as for the general population. During pregnancy, defining a thyroid function testing indication is complicated by the concept that thyroid disease symptoms overlap with those related to a normal pregnancy

and also because mild forms of thyroid disease can present without symptoms. Because thyroid hormone demands are increased in pregnancy, risk factors for maternal thyroid dysfunction can be specific to gestation. Furthermore, the risk of thyroid disease according to general (nonpregnancy) risk factors may be larger during pregnancy as compared with a nonpregnant state. Therefore, we recommend that risk factors for thyroid disease during pregnancy (Table 1) are used to determine the indication for thyroid function testing during pregnancy.

Various studies have shown that risk factors recommended in the previous version of these guidelines would lead to screening of 55–78% of all pregnant women, while detection rates varied between 75% and 85% for overt hypothyroidism and between 54% and 60% for subclinical hypothyroidism.^{53–56} In an effort to optimize these numbers, we commissioned two studies to validate previous risk factors⁵⁷ and to identify new risk factors for thyroid function test abnormalities and TPOAb positivity.⁵⁸ For the risk factors we recommend, the selection of some was supported by good volume and high-quality data (thyroid antibody positivity), while the selection of other risk factors was based on reasonable extrapolation of data from nonpregnant populations (e.g., medication use, Down/Turner syndrome, prior radiation/thyroid surgery, history of autoimmune disease,

iodine deficiency, family history of autoimmune thyroid disease) or expert opinion (remainder). For women with a history of infertility or recurrent miscarriages, we recommend thyroid function testing if this has not already been performed preconception, unless there are other risk factors present, recognizing that women with such history are frequently tested before conceiving. Three specific risk factors were considered but not added as a thyroid function testing indication. A past medical history of a single miscarriage is common and often attributable to nonthyroidal risk factors, and current data are insufficient to consider it as a risk factor for thyroid disease during pregnancy. While BMI and age were recognized as risk factors for thyroid disease during pregnancy (for overt hypothyroidism/isolated hypothyroxinemia and subclinical hypothyroidism, respectively), the absolute risk differences were small and identification of an objective dichotomous cutoff for these variables remains difficult.⁵⁷

It is important to note that the risk factors that are considered an indication for thyroid function testing during pregnancy are not exhaustive. Furthermore, the use of this set of risk factors will not enable the identification of all women with thyroid dysfunction, specifically overt hypothyroidism. Therefore, these risk factors should be used to supplement general clinical reasoning. Similar to the US Preventive Services Task Force recommendations for the general population,⁵⁹ there is insufficient evidence to recommend routine

TABLE 1. RISK FACTORS FOR THYROID DYSFUNCTION DURING PREGNANCY

Risk factor	Suggested TSH testing frequency
History of (subclinical) hypothyroidism/hyperthyroidism including postpartum thyroiditis	At presentation of pregnancy
Known thyroid antibody positivity	Every 4-6 weeks up to mid-pregnancy
Symptoms of thyroid dysfunction or goiter	At presentation of pregnancy
Concurrent medication use associated with thyroid dysfunction ^c	At presentation of pregnancy & every trimester
Personal history of:	
Autoimmune disease ^a	At presentation of pregnancy
Two or more miscarriages ^b	At presentation of pregnancy
Infertility ^b	At presentation of pregnancy
Down syndrome or Turner syndrome	At presentation of pregnancy
Treatment with ionizing radiation to the head and neck region or radioactive iodine	At presentation of pregnancy & every trimester
Prior thyroid surgery	At presentation of pregnancy & every trimester
Family history of autoimmune thyroid disease	At presentation of pregnancy
Residing in an area of severe iodine insufficiency ^d while not using iodine-containing supplements or iodized salt	At presentation of pregnancy & every 4-6 weeks up to mid-pregnancy

^a Including but not limited to type 1 diabetes mellitus, pernicious anemia, celiac disease, Addison's disease, vitiligo, premature ovarian failure, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus

^b Screening is only indicated if it was not performed preconception, or if there are other risk factors present

^c Including but not limited to amiodarone, lithium, rifampin, ethionamide, phenobarbital, phenytoin, carbamazepine, and recent cancer-related immunotherapy (used within 6 months) or iodinated contrast (administered within 2 months)

^d As defined by the Iodine Global Network (<https://www.ign.org>)

thyroid function testing (universal screening) in women planning pregnancy, in pregnant women, or in women during the postpartum period. Detailed overviews of the pros and cons of routine thyroid function testing are described elsewhere.^{60,61}

D. Iodine

Iodine is a trace micronutrient required for thyroid hormone production. There are approximately 15–20 mg of iodine in the human body under normal conditions, with over 70% of this contained in the thyroid gland.⁶² Adequate iodine availability is particularly important in pregnancy, when thyroid hormone requirements are higher, renal iodine excretion is increased, and there is additional demand for iodine from the developing fetus (Figs. 1 and 2).⁶³ Iodine intake should ideally be optimized preconception. For this topic, there is abundant low-to-moderate quality evidence but only sparse high-quality evidence to support recommendations. The committee has assessed all meta-analyses and randomized trials to form recommendations for this subsection, which were often supported by data from single-center observational studies.

Network.⁶⁵ In the United States, data from the National Health and Nutrition Examination surveys show that a substantial portion of pregnant women are iodine insufficient, with median UICs as a population biomarker for iodine status declining since the early 2000s.^{66–69} There is strong evidence that severe maternal iodine deficiency in pregnancy and its effect on thyroid status are associated with adverse obstetrical outcomes, as well as increased risks of maternal and neonatal hypothyroidism, perinatal and infant mortality, low child intelligence quotient (IQ), and child neurocognitive impairment.^{70–74} Data on the adverse effects of mild-to-moderate iodine deficiency in pregnant women are less clear. Mild-to-moderate iodine deficiency has not been associated with adverse obstetric outcomes.^{73,75,76} Observational data show associations between mild/moderate iodine deficiency and impaired fetal brain development.^{77,78} Children of pregnant women with mild-to-moderate iodine deficiency before 14 weeks' gestation had lower IQ scores in a dose-dependent manner.⁷⁹ Adequately powered randomized controlled trials examining child neurodevelopment have not been performed in mild-to-moderate iodine-deficient pregnant women,^{80,81} but it is biologically plausible that neurodevelopmental effects observed in milder forms of iodine defi-

Recommendations Table 3: Iodine Nutrition	Strength*	Level #
Pregnant and lactating women should strive for a daily iodine intake of 250 mcg as provided by dietary iodine intake complemented by iodine supplements as required.	Strong	Moderate
For women at risk of iodine deficiency given geographic region, dietary restrictions or malabsorption, we suggest starting 150 mcg per day iodine supplementation ideally at least 3 months before planned pregnancy and continued until lactation is complete.	Conditional	Moderate
An annual dose of 400 mg iodized oil in women of childbearing age and pregnant women can be given in low-resource countries and/or regions with severe iodine deficiency, where neither salt iodization nor daily iodine supplements are feasible.	Conditional	Moderate
We suggest applying similar iodine supplementation recommendations for pregnant women taking antithyroid drugs (ATDs) for Graves' hyperthyroidism and those taking levothyroxine for hypothyroidism.	Conditional	Low
Excessive iodine exposure during pregnancy should be avoided with the exception of certain medical indications, such as the use of saturated solution of potassium iodide (SSKI) or iodinated contrast media.	Strong	Moderate
Sustained excessive dietary iodine intake and dietary supplements use exceeding 500 mcg daily should be avoided during pregnancy due to concerns for fetal and maternal thyroid dysfunction.	Strong	Moderate

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
ATD, antithyroid drug; SSKI, saturated solution of potassium iodide

What is new in this guideline: In these guidelines, we place greater emphasis on the fact that there remains no valid biomarker for measuring long-term iodine status in an individual person (currently available biomarkers, including urinary iodine concentrations [UICs], are intended only to be interpreted as median levels in populations) and that risk factors for iodine deficiency on the individual-level should continue to be considered when applicable.

Epidemiology and physiology

In 2023, there were 18 countries with insufficient dietary iodine intake out of 127 countries worldwide with available nationally representative data, corresponding to approximately one-third of the world's population^{64,65}; the most current global iodine status data are available from the Iodine Global

ciency can be extrapolated from the literature on severe iodine deficiency. However, in small randomized controlled trials, use of iodine supplementation for women with mild-to-moderate iodine deficiency has not resulted in clinically relevant alterations in maternal and neonatal thyroid function.^{80–85} The sodium/iodide symporter (NIS) plays a crucial role in mediating iodide uptake required not only for thyroid hormone synthesis in both the maternal and fetal thyroid gland but also for the placental transfer of iodide. As such, some of the nutritional effects associated with maternal iodine deficiency could also result in fetal iodine deficiency (Fig. 3).

Clinical presentation and evaluation

The clinical presentation of iodine deficiency would be reflected as hypothyroidism and its sequelae. It is important

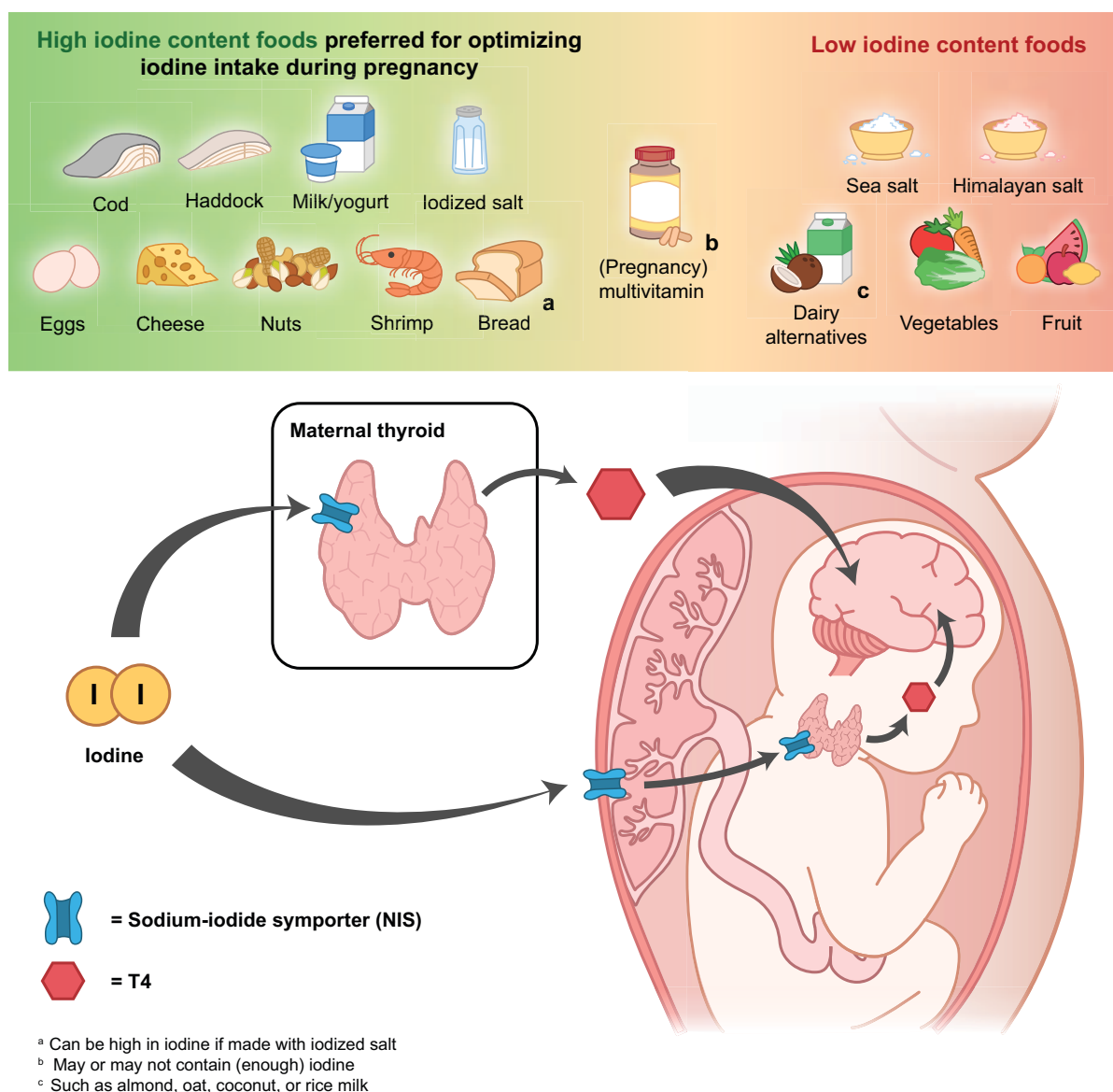


FIG. 3. Iodine availability during pregnancy. Examples of supplements and foods with high and low iodine content are shown. Iodine is taken up by the NIS at the basolateral membrane of the thyroid follicular cell in both the mother and fetus, as needed for thyroid hormone production, for which requirements are higher during pregnancy. NIS, sodium/iodide symporter.

to note that there are no validated biomarkers to assess chronic iodine intake on the individual level. Instead, iodine status is measured across populations and is usually assessed by median spot or 24-hour UICs; median UIC values between 100 and 199 mcg/L indicate population iodine sufficiency among nonlactating, nonpregnant women, while median UICs between 150 and 249 mcg/L indicate optimal iodine nutrition in pregnant populations.

Other available measures for assessing population iodine status include serum or whole-blood thyroglobulin concentrations and neonatal TSH concentrations.⁸⁶ Serum or whole-blood thyroglobulin values have been proposed for assessing iodine status of populations of pregnant women,⁸⁷ but there is currently no consensus on their threshold values, and poor harmonization between assays further limit their utility.^{86,88} Neonatal TSH concentrations may be available in regions where these measurements are used to screen for congenital

hypothyroidism and may be higher in iodine-deficient regions. The prevalence of neonatal TSH concentrations greater than 5.0 mU/L should be <3% in iodine-sufficient regions.⁸⁹ However, the timing of assessing neonatal TSH relative to the neonatal TSH surge, as well as the use of iodophor cleansers at the time of delivery, may limit the utility of neonatal TSH as a marker for population iodine nutrition. Finally, there is a substantial degree of intraindividual variation in the ability of the thyroid gland to adapt to insufficient iodine availability, even in those living in severely iodine-deficient regions. Therefore, serum thyroid function tests are not considered sensitive indicators of population iodine status in most groups, including pregnant and postpartum women.⁹⁰

Although the World Health Organization suggests a median UIC threshold of >100 mcg/L to indicate adequate iodine nutrition in lactating women, UIC alone may not fully reflect the iodine status of this group, as UIC tends to be lower in lactating women compared with nonlactating

women, since iodine is excreted both in urine and breast milk (Fig. 4).⁹¹ Thus, spot breast milk iodine concentrations have also been considered as a biomarker of iodine status in lactation. Breast milk iodine content (BMIC) reflects recent iodine intake, but there is intraindividual variability. Cross-sectional studies have suggested that a median BMIC range of 100–200 mcg/L is considered adequate in lactating women⁹²; however, no formal

minimal threshold has been established. As such, the optimal metric for assessing the iodine status in populations of lactating women is currently unclear.⁹²

Treatment and management

Pregnant and lactating women are recommended to receive a total of 250 mcg iodine daily as provided by

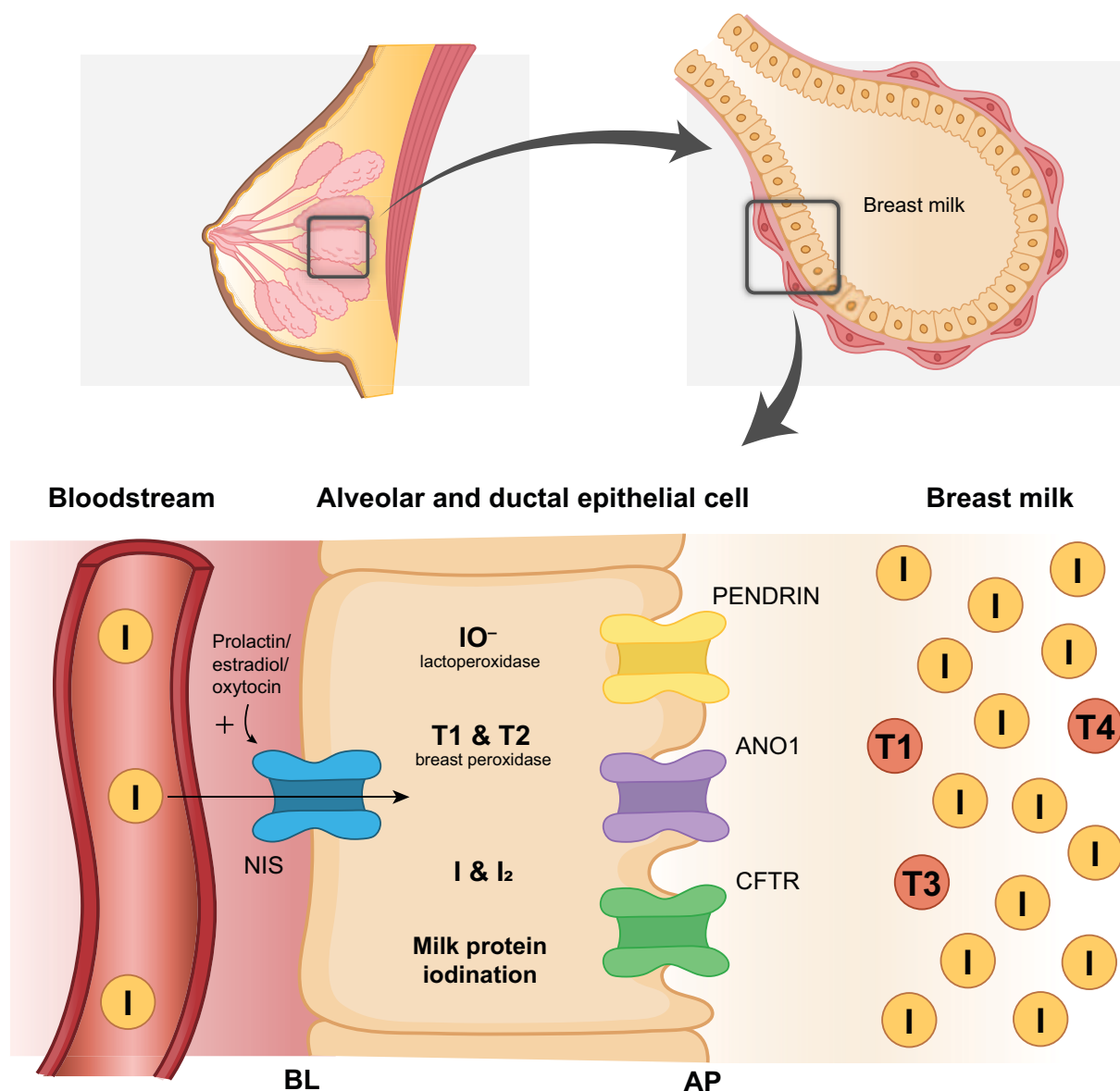


FIG. 4. Thyroid hormone and iodine content in breastmilk. Although the World Health Organization suggests a median UIC threshold of >100 mcg/L to indicate adequate iodine nutrition in lactating women, UIC alone may not fully reflect the iodine status of this group, as UIC tends to be lower in lactating women compared with nonlactating women, since iodine is excreted both in urine and breast milk. NIS and Pendrin are expressed in lactating mammary cells and facilitate the uptake of iodine from maternal circulation into breastmilk. Iodide transport across the apical epithelial membrane also occurs through transporters that include ANO1 and CFTR. Limited data suggest that iodine occurs in various forms in breastmilk, mostly iodide (~77%) and other organic materials like iodinated milk proteins (~11%). It also occurs in thyroid hormones, predominantly T1 (~7–25%) but very little T4 or T3 (~1%; no data on T2).³⁵⁴ The maximum methimazole/carbimazole content of breast milk is 0.1–0.2% of the maternal dose, and for PTU, this is <0.1%.^{342,343} AP, apical; ANO1, anoctamin-1; BL, basolateral; CFTR, cystic fibrosis transmembrane conductance regulator; PTU, propylthiouracil; T3, triiodothyronine; T4, thyroxine; UIC, urinary iodine concentration.

iodine supplements and/or dietary iodine intake.⁹¹ Ensuring adequate iodine status as a public health measure is best achieved when iodine supplementation is advised for women in general during these life stages, not just those residing in at-risk areas. However, strategies for optimal iodine intake vary by geographic region. Iodine supplementation of 150 mcg/day should be advised in all women preconception, in pregnancy, and lactation (unless there is high iodine intake evident due to traditional dietary habits) and ideally beginning at least 3 months before conception. Women may need higher amounts of supplementation if at increased risk for iodine deficiency based on information about population iodine status in the region or dietary patterns in the woman (Fig. 3; e.g., not using iodized salt, not ingesting dairy foods, following a vegan diet).⁹³ The supplemental iodine doses reported in the literature to assess their effects on obstetric and offspring outcomes have ranged from 50 to 300 mcg/day, in line with the range of region-specific background dietary iodine intakes of the various populations studied.^{72,80,81} In low-resource countries and regions where neither salt iodization nor daily iodine supplements are feasible, the most vulnerable populations for iodine deficiency can be protected by providing an annual dose of 400 mg iodized oil to pregnant women and women of childbearing age.^{91,94} It should be noted that this should not be used as a long-term strategy or in regions where other options for adequate iodine nutrition are available.

Finally, excess iodine exposure during pregnancy should also be avoided, except in preparation for the surgical treatment of Graves' disease (when saturated solution of potassium iodide may be used) and when potassium iodide is used as an alternative treatment for Graves' disease during pregnancy (in which potassium iodide of up to 50 mg/day has been described).^{95,96} Clinicians should carefully weigh the risks and benefits when ordering medications or diagnostic tests that will result in high iodine exposure (e.g., amiodarone or iodinated contrast media) during pregnancy. Amiodarone is currently classified by the US Food and Drug Administration to pose possible human fetal risk, although it is recognized that its potential benefits may warrant use of the drug in pregnant women. In particular, sustained excessive dietary iodine intake and dietary supplements use exceeding 500 mcg daily should be avoided during pregnancy, due to concerns for fetal and maternal thyroid dysfunction.⁹⁷

E. Thyroid Dysfunction and Infertility

The approach to assessment and management of thyroid disease in women with infertility and/or recurrent miscarriages is largely similar to that for the general population. However, this group may benefit from a more proactive approach to diagnosis and treatment. There are notable differences between women with infertility (or those planning fertility treatment) and the general population, including several key distinctions: (1) the window of opportunity to conceive is often shorter for women with infertility, (2) there are time constraints imposed by fertility treatments, and (3) fertility treatments are associated with increased thyroid hormone demand. Optimal thyroid care requires timely diagnosis following the first presentation of a thyroid function test abnormality, as well as anticipation of pregnancy-specific physiological alterations in thyroid function, disease, and treatment. For this topic, there is abundant low-to-moderate quality evidence but only sparse high-quality evidence to support recommendations. The committee has assessed all meta-analyses and randomized trials to form recommendations for this subsection, which were often supported by data from single-center observational studies. Dependent on the availability of evidence, some recommendations specifically mention women with recurrent miscarriages if data were available. While the group of women with recurrent miscarriages was not specifically defined during the design of the methodology supporting this guideline, it is reasonable to also apply all other recommendations in this subsection to women with recurrent miscarriages.

What is new in this guideline: (1) For women who are euthyroid but TPOAb positive, LT4 treatment should not be offered to women with infertility, those planning fertility treatment, or those with a history of recurrent miscarriages. Instead, thyroid function may be checked every 3–6 months preconception as there remains a 7–9% risk of developing overt or subclinical hypothyroidism before or during pregnancy. This is based on three high-quality randomized trials that have been published since the previous guidelines. (2) For subclinical hypothyroidism, diagnostic confirmation with repeat thyroid function testing may be considered before LT4 treatment, because many women with a single abnormal TSH will have a normal TSH upon retesting.

Thyroid function testing and monitoring in infertility

Recommendations Table 4: Thyroid Function Testing and Monitoring in Women with Infertility		Strength*	Level #
TSH testing should be performed in all non-pregnant women who present with infertility or recurrent miscarriages.		Good Practice Statement	
TPOAb testing may be performed in all women who present with infertility or recurrent miscarriages.		Conditional	Low
For women with infertility or recurrent miscarriage who are taking levothyroxine, utilize a target TSH of 0.5-2.5 mU/L preconception and in pregnancy.		Good Practice Statement	
For women using levothyroxine, TSH may be checked once within 6-12 weeks prior to controlled ovarian stimulation, approximately two weeks after a positive pregnancy test and then according to pregnancy recommendations (see elsewhere).		Conditional	Low

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TSH, thyroid stimulating hormone; TPOAb, thyroperoxidase antibody

Overt hypothyroidism in infertility

Recommendations Table 5: Overt Hypothyroidism in Women with Infertility		Strength*	Level #
In women with newly diagnosed or uncontrolled overt hypothyroidism, fertility treatment should be delayed until euthyroidism is restored.		Good Practice Statement	
Women with overt hypothyroidism who are planning pregnancy should be treated with levothyroxine (LT4).		Strong	Moderate
Thyroid preparations other than levothyroxine (LT4), such as liothyronine (LT3) or desiccated thyroid extract, should not be used in women planning pregnancy.		Strong	Low

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
 LT4, levothyroxine; LT3, liothyronine

It is important to emphasize that the definition of thyroid dysfunction in women with infertility or those undergoing fertility treatment is the same as that of the general population and thus should be defined according to local reference intervals that are used for the general population. There are two main arguments that support thyroid function testing in women with infertility or history of recurrent miscarriage. First, overt and subclinical hypothyroidism are part of their differential diagnosis (for infertility mainly, in a woman presenting with irregular menses). Second, it has been proposed that overt and subclinical hypothyroidism could be an indication for LT4 treatment in this specific subgroup, as fertility outcomes may be improved and progression from subclinical to overt hypothyroidism can be avoided.

There is value in determining TPOAb status in women with infertility or history of recurrent miscarriage. Approximately 7–9% of euthyroid TPOAb-positive women develop overt or subclinical hypothyroidism during follow-up, mostly in the one year before conception but also during gestation.^{98–100} Even though LT4 treatment is not indicated for euthyroid TPOAb positivity, TPOAb measurement as part of thyroid function testing is valuable for identifying those more likely to develop hypothyroidism and, therefore, more likely to require LT4 treatment in the near future. The TPOAb status also has some prognostic value for the risk of miscarriage, preterm birth, and PPT. The cost for implementation and a lack of a proven benefit of intervention are the primary arguments against routine TPOAb testing. In view of this, an individualized approach to TPOAb testing may be warranted, where women with a higher likelihood of having antibodies can be considered for testing. This may include women with high-normal TSH concentrations, history of recurrent miscarriages, other autoimmune diseases, or a first-degree relative with thyroid autoimmunity.^{24,101,102} Robust cost-effectiveness analyses are needed to determine the true cost implications of preconception routine thyroid antibody testing.

For any woman taking LT4 and planning pregnancy, a TSH between 0.5 and 2.5 mU/L is a reasonable treatment target. This strategy creates a margin of safety for maintaining a euthyroid state in anticipation of the increased thyroid hormone demand and LT4 dose adjustments that occur during ovarian stimulation and pregnancy. It is important to note that variations of preconception TSH concentrations within the reference interval do not affect fertility or pregnancy outcomes or the effectiveness of LT4 treatment to a clinically relevant extent.^{100,103–106}

Epidemiology and physiology. The prevalence of undiagnosed overt hypothyroidism in women with a history of infertility or recurrent miscarriages is approximately 0.2%, which is similar to that in women of childbearing age in the general population.^{101,107} The main risk factor for overt hypothyroidism is thyroid autoimmunity; around 70% of all women with overt hypothyroidism detected in the setting of the work-up for infertility or recurrent miscarriages are TPOAb positive.¹⁰¹ Furthermore, hypothyroidism is more common in women with other autoimmune diseases. This is particularly relevant for autoimmune diseases that are part of multiple autoimmune endocrinopathies,^{38,108,109} and it can be beneficial to further investigate any sign of such abnormalities in anticipation of pregnancy. Greater age is also associated with a higher risk of overt hypothyroidism, and there are considerable regional and interpopulation (ethnicity-based) differences in the prevalence of hypothyroidism.^{38,107,109,110}

Clinical presentation, evaluation, and management. The evaluation and management of overt hypothyroidism in women with a history of infertility is the same as that of the general population,¹¹¹ although the clinical presentation may be more atypical (Box 2). Overt hypothyroidism is a well-established risk factor for infertility or recurrent miscarriages through a multifactorial pathogenesis that includes metabolic, endocrine, and menstrual disturbances.⁹ Untreated overt hypothyroidism presents with menstrual disturbances in about 23% of cases (mainly as amenorrhea, hypomenorrhea, and menorrhagia), while hypothyroidism accounts for 2–3% of all causes of anovulation.^{112,113} Data on fertility outcomes in women with untreated hypothyroidism remain sparse as LT4 treatment is usually started without delay. More importantly, women with pre-existing hypothyroidism, who are euthyroid on LT4 treatment, have the same fertility outcomes as those without hypothyroidism.^{9,114,115} Assessing risk factors for iodine deficiency is helpful to determine an indication for iodine supplementation to prevent maternal and fetal hypothyroidism. Iodine supplementation is preferably started preconception (see Section D). In addition, checking TPOAb status is useful for etiological and prognostic purposes. Women using liothyronine or desiccated thyroid extract preparations should be recommended to switch to LT4 monotherapy before starting fertility treatment to avoid insufficient thyroid hormone availability for the fetal brain (see Section F).

Box 2. Practical considerations for managing thyroid dysfunction in women with infertility or undergoing fertility treatment

- It is advised to reassess the patient's fertility treatment plans and schedule (e.g., ovarian stimulation and embryo transfer) at each visit because these can change throughout the fertility treatment pathway, and these changes may require adjustment of thyroid treatment and/or follow-up planning accordingly.
- There are substantial changes to thyroid physiology during fertility treatment, in particular during ovarian stimulation (Figure 1A), which may make interpretation of thyroid function tests more difficult. Therefore, it is sensible to refrain from obtaining thyroid function tests during ovarian stimulation or within 2 weeks of an ovulation trigger.
- In women on levothyroxine, increases in estrogen from ovarian stimulation can lead to an earlier increase in levothyroxine requirements compared to in women who conceive naturally. The extent of estrogen increase and levothyroxine requirements are partly determined by the duration and intensity of ovarian stimulation. It is reasonable to anticipate this physiology and check thyroid function tests two weeks after a positive pregnancy test.
- The majority of thyroid dysfunction in women with infertility and/or planning fertility treatment is identified through a routine work-up for the underlying cause of fertility treatment. Therefore, it is more likely to detect a latent phase of disease, which may present in an atypical manner as compared to patients who present with symptoms.
- Thyroid function testing should be assessed upon presentation of thyrotoxic symptoms in women undergoing fertility treatments, as painless thyroiditis and Graves' disease may be induced by gonadotropin-releasing hormone analogues or following a miscarriage.¹¹⁶⁻¹²¹

Subclinical hypothyroidism in infertility

Recommendations Table 6: Subclinical Hypothyroidism in Women with Infertility	Strength*	Level #
In women with newly diagnosed or uncontrolled subclinical hypothyroidism, fertility treatment may be delayed until the spontaneous restoration or therapy-induced restoration of euthyroidism.	Conditional	Low
Subclinical hypothyroidism with a TSH >10 mU/L should be treated with levothyroxine.	Good Practice Statement	
For all women with newly diagnosed subclinical hypothyroidism, diagnostic confirmation with rechecking TSH and FT4 may be done in 4-6 weeks.	Conditional	Moderate
If the TSH concentration normalizes upon repeat measurement:	Conditional	Low
1) TPOAb negative women do not require biochemical follow-up and may be advised to seek medical evaluation upon the development of hypothyroid symptoms. 2) TPOAb positive women may be followed-up with TSH testing every 3-6 months when planning pregnancy, and once pregnant, every 4-6 weeks during the first half of pregnancy, at least once in the third trimester, and 4-6 weeks after any dose adjustment.		
If subclinical hypothyroidism is persistent upon repeat testing:	Conditional	Low
1) Low dose (25-75 mcg/day) levothyroxine may be started, with a TSH measurement after 4-6 weeks and levothyroxine dose titrated to a target TSH between 0.5-2.5 mU/L.		

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TSH, thyroid stimulating hormone; FT4, free thyroxine; TPOAb, thyroperoxidase antibody

Epidemiology and physiology. The prevalence of undiagnosed subclinical hypothyroidism in women with infertility or recurrent miscarriages is approximately 2.4%, which is similar to that of women of childbearing age in the general population.^{101,120-123} The main risk factor for subclinical hypothyroidism is thyroid autoimmunity; about 40% of all women with subclinical hypothyroidism, detected in the setting of the diagnostic work-up for infertility or history of recurrent miscarriages, are TPOAb positive, and this rises to 80% for those with a TSH >10 mU/L.^{101,108} Other risk factors include obesity, and considerable regional and inter-population differences in the prevalence of subclinical hypothyroidism occur.^{101,107}

Clinical presentation, evaluation, and management. The clinical presentation, evaluation, and management of subclinical hypothyroidism in women with a history of infertility are largely similar to those of the general population.¹¹¹

The majority of women with infertility who are diagnosed with subclinical hypothyroidism are diagnosed in the work-up for infertility and are asymptomatic. In these women especially, it is difficult to assess whether subclinical hypothyroidism represents normal population variation in TSH or an early form of overt hypothyroidism. Assessing risk factors for iodine deficiency and checking TPOAb status is useful for etiological, therapeutic, and prognostic purposes, as well as determining the frequency of follow-up during a future pregnancy.

It is well-established that the diagnosis of subclinical hypothyroidism is complicated by large interindividual and intraindividual variations in TSH.^{124,125} In older populations, up to 80% of mildly increased TSH concentrations may spontaneously normalize upon remeasurement.¹²⁶ It is good clinical practice to repeat thyroid function tests after the first identification of subclinical hypothyroidism, because reducing inappropriate LT4 treatment is important to prevent

unnecessary patient anxiety, costs, burden on the health care system, and risks related to overtreatment.^{125,127} In women with infertility, those undergoing fertility treatment, and women with recurrent miscarriages, we recommend aiming for diagnostic confirmation upon first identification of subclinical hypothyroidism by rechecking TSH and fT4 after four to six weeks while delaying fertility treatment. If there is persistent subclinical hypothyroidism, LT4 therapy may be started. In cases of spontaneous normalization of TSH, the TPOAb status can be used to identify patients who may benefit from additional biochemical follow-up. TPOAb positivity is a risk factor for progression to overt hypothyroidism

time constraints related to the age of the patient, the presence of other comorbidities, or due to financial reimbursement related issues. Furthermore, repeat testing may not be deemed pragmatic when there is a low likelihood of TSH normalization. Specific examples would be when the TSH concentration is relatively high (for which the task force suggests a TSH cutoff of 6 mU/L) or when there is concomitant TPOAb positivity.^{51,52} In those cases, it would be sensible to offer immediately low-dose LT4 (25–75 mcg/day) following a shared decision-making approach.

Thyroid autoimmunity in infertility

Recommendations Table 7: Thyroid Autoimmunity in Women with Infertility	Strength*	Level #
For euthyroid TPOAb and/or TgAb positive women with infertility, levothyroxine treatment should not be offered. ^a	Strong	High
For euthyroid TPOAb and/or TgAb positive women planning pregnancy, TSH and FT4 may be rechecked every 3-6 months.	Conditional	Low
For TPOAb and/or TgAb positive women with infertility, do not offer oral prednisolone or intravenous immunoglobulin treatment.	Conditional	Low

^a Regardless of TSH concentration or miscarriage history

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TPOAb, thyroperoxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid stimulating hormone; FT4, free thyroxine

Dissenting comments for Recommendations Table 7 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

and an indication for TSH monitoring preconception and during pregnancy.^{98,100,105} For TPOAb-negative women, we advise instructing the patient to seek medical evaluation upon the development of any hypothyroid symptoms. For cases where the physician remains uncertain (e.g., due to a borderline TSH concentration upon retesting, the presence of hypothyroid symptoms, or a high-normal TPOAb titer), it is reasonable to continue evaluation and monitoring, which may include thyroglobulin antibody (TgAb) testing following a shared decision-making approach.

Meta-analyses and narrative reviews, including low-quality studies, conclude that untreated preconception subclinical hypothyroidism in the general population is associated with various mild endocrine changes,⁹ a slightly lower chance of conception (absolute difference: –1.4% to –4.5% for increased TSH but <10 mU/L), and a slightly higher risk of miscarriage (absolute difference: +0.4% to +0.7% for increased TSH but <10 mU/L),¹⁰⁴ with similar numbers for women undergoing ART.^{128,129} In one small, low-quality Korean randomized trial including 64 women, LT4 treatment started on the first day of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment in women with subclinical hypothyroidism improved the embryo implantation rate (15% vs. 27%), miscarriage rate (33% vs. 0%), and live birth rate (25% vs. 53%).¹³⁰ Women with infertility and those undergoing fertility treatment who have persistent subclinical hypothyroidism preconception could benefit from LT4 treatment as this could prevent progression to overt hypothyroidism, which is especially relevant as there is a state of increased thyroid demand during controlled ovarian stimulation and pregnancy.

The task force recognizes that for certain cases of newly diagnosed subclinical hypothyroidism, verifying persistence is not possible or pragmatic. This can occur in the setting of

This section focuses on TPOAb positivity in women with infertility (considerations related to TgAb positivity in women with infertility can be found in Box 4). TPOAb positivity has a better diagnostic accuracy for hypothyroidism than TgAb positivity and is associated with adverse fertility and pregnancy outcomes, unlike TgAb positivity. Therefore, a TPOAb measurement remains the preferred test to establish or risk stratify for autoimmune hypothyroidism. Assessing TgAb positivity is at the discretion of the physician but can be considered in certain cases (e.g., a euthyroid TPOAb-negative woman with a high-normal TSH and a high risk of thyroid autoimmunity based on previous thyroiditis, concomitant autoimmune disease, or having a first-degree relative with thyroid autoimmunity). Although it is reasonable to also apply recommendations in this subsection to TgAb positive women, this group was not specifically defined during the design of the methodology supporting this guideline.

Epidemiology and physiology. The prevalence of TPOAb positivity in women with infertility or those with a previous miscarriage is around 8–11%, which is similar to that of women of childbearing age and pregnant women in the general population.^{24,57,101,102,105,106} The prevalence may be about twice as high in women with recurrent miscarriages.¹³¹ Risk factors for TPOAb positivity include other autoimmune diseases, a first-degree relative with thyroid autoimmunity, greater age, obesity, and nulliparity, while smoking is associated with a lower risk and considerable variation is reported by geographical area and/or ethnicity.^{24,101,102,132} Thyroid autoimmunity can reduce the functional capacity of the thyroid gland, and this can become apparent during states of increased thyroid demand. However, in euthyroid TPOAb-positive women, TSH concentrations during controlled ovarian stimulation are comparable to those in euthyroid TPOAb-negative women.¹⁹

Clinical presentation, evaluation, and management. The clinical presentation and evaluation of TPOAb positivity depend on thyroid function and are similar to those of the general population.¹¹¹ Euthyroid TPOAb positivity does not present with symptoms. Thyroid autoimmunity is the main risk factor for hypothyroidism. In randomized trials, approximately 7–9% of euthyroid TPOAb-positive women developed (subclinical) hypothyroidism during a 12-month follow-up; cases were mostly detected preconception but also during pregnancy.^{98–100} Therefore, it seems prudent to recheck TSH every three to six months in euthyroid TPOAb-positive women who are planning a pregnancy.

Euthyroid TPOAb positivity is associated with a higher risk of miscarriage and PPT, and the latter can also occur after a miscarriage.^{100,105,106,133,134} The absolute risk difference for a miscarriage as compared with TPOAb-negative women ranges from about +2% to +8%, but there are no data for the risk of thyroiditis after miscarriage.^{105,134–136}

Since the publication of the previous version of these guidelines, three high-quality randomized trials have shown that for euthyroid TPOAb-positive women with infertility and/or a history of prior/recurrent miscarriage(s), LT4 therapy given during preconception does not improve fertility or pregnancy outcomes.^{100,105,106} We extrapolated these results, obtained in a high-risk population, to make recommendations for the general population. There were no factors that modified the response to LT4 treatment, including a TSH >2.5 mU/L, previous miscarriage(s), maternal age, or the TPOAb concentration.^{100,105,106,135,137,138} This suggests that the mechanism underlying the higher risk of miscarriage and other adverse fertility outcomes in euthyroid TPOAb-positive women is not mediated through changes in thyroid hormone availability and remains to be elucidated. It is plausible that thyroid antibodies are a reflection of a more general susceptibility to autoimmunity and that other autoimmune processes are underlying the higher risk of pregnancy complications.¹³⁹ However, there are currently no data to support a dietary intervention or the use of immune modulatory medications, such as glucocorticoids, intravenous immunoglobulins, or selenium, to improve obstetric outcomes or lower the risk of developing hypothyroidism (during pregnancy).

Subclinical and overt hyperthyroidism in infertility

or recurrent miscarriages. First, it is relevant to assess the schedule and timing of fertility treatments since (age-dependent) time constraints may warrant a faster diagnostic and/or therapeutic route than usual care. This concept applies to any woman with thyroid disease who is planning pregnancy but can be more relevant for those with subclinical and overt hyperthyroidism owing to the required diagnostics and longer time to reach euthyroidism. Second, for sporadic cases in which the TSH remains persistently suppressed to <0.1 mU/L and both fT4 and T3 are normal, yet no clear underlying cause can be identified after a regular work-up, intensified follow-up during preconception and pregnancy can be considered to identify the possible progression of hyperthyroidism at an early phase. Alternatively, it may be reasonable to consider low-dose propylthiouracil (PTU) preconception. The goal of this approach would be to normalize the TSH concentration prior to pregnancy. This is based on expert opinion and supported by a large observational study showing that a suppressed TSH is associated with a delayed time to pregnancy in untreated women.¹⁰⁴ PTU can be stopped upon a positive pregnancy test to reduce the risk of fetal birth defects associated with PTU exposure, and the patient should be instructed to do so immediately or seek contact upon a positive pregnancy test. If only cryopreservation of oocytes or embryos is planned without the anticipation of an embryo transfer in the immediate future, ATDs can be continued before and during the fertility preservation treatment.

F. Hypothyroidism, Thyroid Autoimmunity, and Hypothyroxinemia Preconception and In Pregnancy

The approach to hypothyroidism during pregnancy differs based on the timing of the diagnosis (preconception vs. gestational) and the magnitude of the thyroid function test abnormality (overt vs. subclinical disease and/or degree of TSH elevation). Laboratory values are the main determinant of general management because of the frequent lack of hypothyroid symptoms during pregnancy and the overlap of hypothyroid symptoms with those of a healthy pregnancy. Optimal management requires anticipation of known physiological gestational alterations of thyroid function parameters, as well as knowledge regarding the interpretation of labora-

Recommendations Table 8: Subclinical and Overt Hyperthyroidism Preconception		Strength*	Level #
Diagnostic confirmation of subclinical hyperthyroidism in women with infertility should be performed by rechecking TSH and FT4 after 4-6 weeks.		Good Practice Statement	
Overt hyperthyroidism in women with infertility should be treated preconception, either according to the underlying cause or with a low dose of antithyroid drugs if no underlying cause can be identified.		Good Practice Statement	

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TSH, thyroid stimulating hormone; FT4, free thyroxine

The epidemiology, physiology, clinical presentation, evaluation, and management of preconception subclinical and overt hyperthyroidism are discussed in Section G. For this subsection, we briefly highlight two considerations specifically for women with subclinical or overt hyperthyroidism who are planning pregnancy in the setting of infertility and/

tory tests (see Section C). Furthermore, clinicians should be knowledgeable about (absolute) risks of thyroid dysfunction, to provide individualized counseling on the pregnancy complications or adverse child outcomes risks related to (subclinical) hypothyroidism and the potential benefits of LT4 treatment.

What is new in this guideline: (1) TPOAb status is no longer used to guide LT4 treatment decision-making in women with subclinical hypothyroidism. This is because differences in the risk of adverse outcomes between TPOAb-positive and TPOAb-negative subclinical hypothyroidism are small, and new data from randomized trials show no benefit of treating euthyroid TPOAb positivity. (2) Indication for, or consideration of, LT4 treatment should now be determined according to the timing of subclinical hypothyroidism diagnosis. This is because data from randomized trials and observational studies indicate that LT4 treatment started after approximately the first trimester does not improve the risks of adverse pregnancy or child neurocognitive outcomes. (3) We emphasize repeat thyroid function testing to verify that mild (i.e., a TSH <6 mU/L) overt hypothyroidism or subclinical hypothyroidism is persistent. The absolute risk increase for adverse pregnancy or child outcomes is generally small for mild overt hypothyroidism and subclinical hypothyroidism. There is no established evidence of any harm related to a short delay in the start of LT4 treatment. Furthermore, recent data indicate that at least half of these thyroid function test abnormalities spontaneously normalize within a few weeks, suggesting that remeasurement can reduce overdiagnosis, overtreatment, and associated harms.

Overt hypothyroidism in preconception and pregnancy

childbearing age,^{101,107} and new-onset overt hypothyroidism occurs in approximately 0.4–0.5% of all pregnant women,^{57,110} although the prevalence during pregnancy largely depends on the upper limit used for TSH (laboratory-specific vs. a fixed limit).^{38,57,110} The main risk factor for hypothyroidism before or during pregnancy is thyroid autoimmunity, with hypothyroidism being more common in women with other autoimmune diseases, especially those autoimmune diseases that are a part of multiple autoimmune endocrinopathies.^{38,108,109} Greater age is associated with a higher risk of preconception hypothyroidism but not with hypothyroidism during pregnancy, and considerable regional and interpopulation (ethnicity-based) differences in hypothyroidism prevalence occur.^{38,107,109,110} It remains unknown what proportion of hypothyroidism during pregnancy is pre-existing disease identified for the first time during pregnancy versus gestation-specific hypothyroidism related to the increased thyroid hormone demand of pregnancy.

Clinical presentation and evaluation. The clinical presentation and evaluation of hypothyroidism outside of the perinatal period are summarized in detail elsewhere.¹¹¹ Most women diagnosed with overt hypothyroidism during pregnancy are identified when presenting for general obstetric care. While overt hypothyroidism

Recommendations Table 9: Overt Hypothyroidism Preconception and in Pregnancy		Strength*	Level #
For new onset maternal overt hypothyroidism during pregnancy with a TSH less than 6 mU/L, confirmatory testing may be performed within 3 weeks to verify an indication for levothyroxine treatment.		Conditional	Low
New onset maternal overt hypothyroidism during pregnancy with a TSH equal or above 6 mU/L, or overt hypothyroidism that persists after retesting should be treated with levothyroxine.		Strong	Moderate
Maternal hypothyroidism during pregnancy should be treated with levothyroxine monotherapy. Other thyroid preparations such as LT3 or desiccated thyroid should not be used in pregnancy.		Strong	Low

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TSH, thyroid stimulating hormone, LT3, liothyronine

In women known to have hypothyroidism prior to pregnancy, the basis of disease management during the preconception, gestational, and postpartum periods is similar to the general recommendations for nonpregnant patients. Some additional considerations specific to these periods, based on established clinical practice rather than high-quality evidence, are outlined in Box 3. Longstanding overall agreement to treat overt hypothyroidism during pregnancy with LT4 has limited the synthesis of evidence on the risks of untreated hypothyroidism and the benefits of treatment. Most available data on overt hypothyroidism during pregnancy are from studies published 20–30 years ago and therefore include more severe cases than those typically detected in current clinical practice. Nonetheless, LT4 treatment benefits are still considered to outweigh any risks. In general, women with hypothyroidism who remain euthyroid with LT4 treatment have similar fertility, pregnancy, and postpartum outcomes as women without hypothyroidism.

Epidemiology and physiology. The prevalence of overt hypothyroidism is approximately 0.2% of all women of

during pregnancy is associated with more hypothyroid symptoms than in euthyroid women, this difference is not large enough to distinguish between the groups, and many women with overt hypothyroidism in pregnancy present without symptoms.^{140,141} Assessing risk factors for iodine deficiency is helpful to determine an indication for iodine supplementation, since iodine deficiency could cause maternal hypothyroidism and sustained fetal hypothyroidism (Section D). In addition, checking TPOAb status in those with new-onset overt hypothyroidism is useful for etiological and prognostic purposes and for determining the frequency of follow-up during the remainder of pregnancy or during a future pregnancy. Untreated or inadequately controlled hypothyroidism during pregnancy is associated with a higher risk of miscarriage, gestational hypertension, preterm birth, and up to seven points lower mean offspring IQ.^{142–147} However, it is difficult to quantify these risks for counseling purposes in current clinical practice because these data were collected at least 15–25 years ago and

Box 3. Preconception and gestational considerations for the management of hypothyroidism

Preconception

- Active assessment of a woman's desire to become pregnant and/or advising patients to seek guidance for a future pregnancy will optimize preconception and gestational management of hypothyroidism.
- If levothyroxine treatment establishes biochemical euthyroidism, the chance of conception is optimized and the risk of adverse fertility/pregnancy outcomes is similar to women without hypothyroidism.
- If treated with levothyroxine, a preconception TSH target of 0.5-2.5 mU/L can be used to lower the risk of undertreatment during fertility treatments and/or early pregnancy.
- It is reasonable to temporarily increase the thyroid function testing frequency to once every 3-6 months in women with treated hypothyroidism who are trying to conceive.

Gestational

- Most women will require a levothyroxine dose increase of approximately 25% by week 12 and 50% by week 20, and the levothyroxine dose should thus be increased by about 25% upon a positive pregnancy test considering the half-life of levothyroxine. However, overtreatment with this approach is possible (see text).
- A typical monitoring strategy in women with treated hypothyroidism would include thyroid function testing every 4 weeks until midgestation and at least once near 30 weeks gestation.

TSH, thyroid stimulating hormone

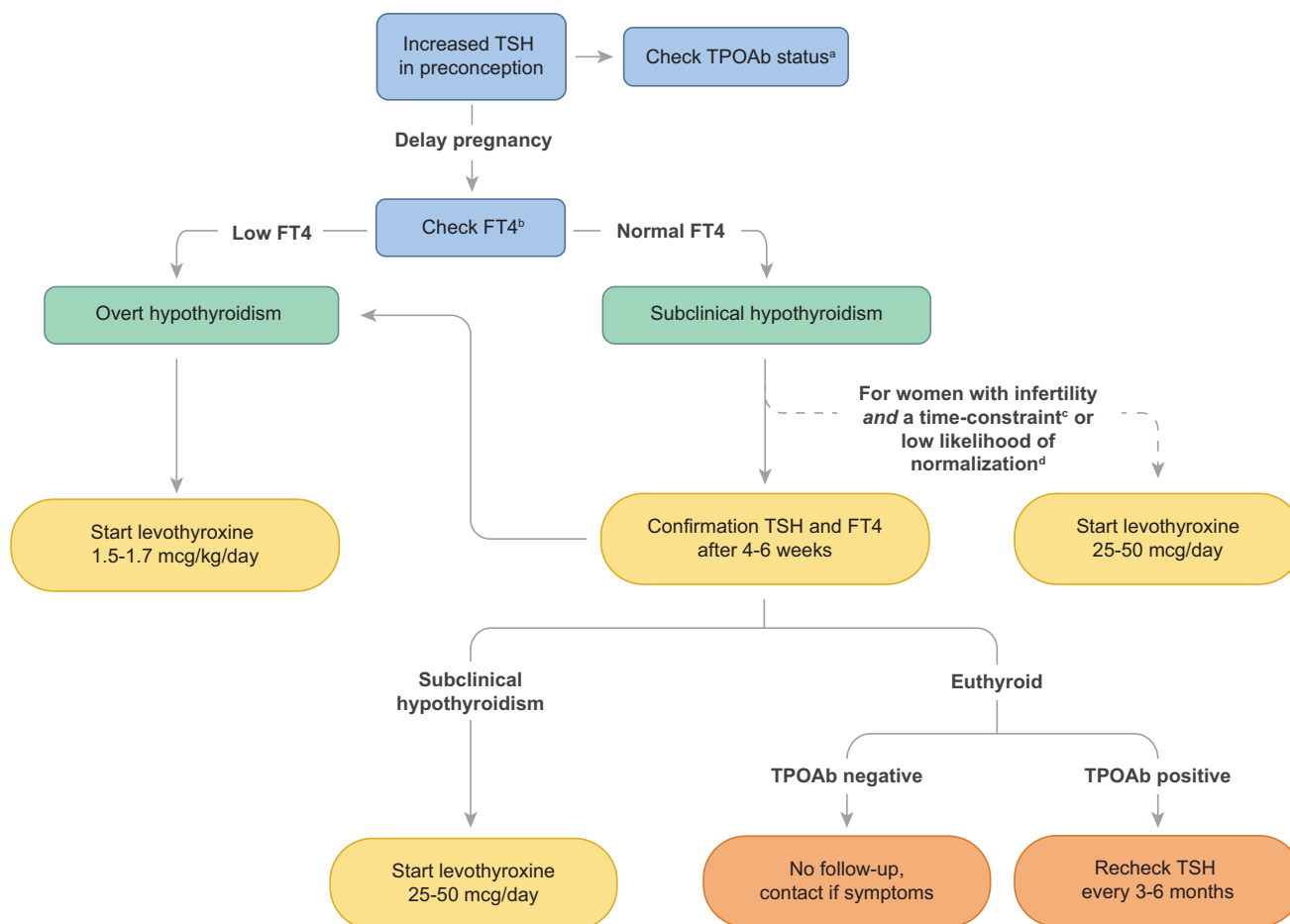
studies may be biased. Within the group of women with overt hypothyroidism during pregnancy, a higher TSH concentration is associated with a higher risk of miscarriage and lower offspring IQ,^{146,147} but no other factors are known to modify the risk of adverse outcomes. Newly diagnosed overt hypothyroidism during pregnancy is not considered a medical reason for termination of pregnancy.^{148,149} Women with pre-existing hypothyroidism who adhere to LT4 treatment and/or those with hypothyroidism diagnosed during pregnancy who achieve biochemical control with LT4 have similar risks of adverse pregnancy or child outcomes as women without hypothyroidism during pregnancy.^{144,145,147-152}

Preconception treatment and management. The management of hypothyroidism outside of the perinatal period is summarized in detail elsewhere,¹¹¹ and preconception recommendations specifically for women with infertility can be found in Section E. The guidance for the management of overt and subclinical hypothyroidism in women planning pregnancy is summarized in Flowchart 1 and for pregnant women in Flowchart 2. Following an established diagnosis, a logical LT4 treatment target for a woman wishing to conceive is a TSH in the reference interval but below 2.5 mU/L, in order to create a margin of safety for remaining euthyroid in anticipation of a state of increased thyroid hormone demand during pregnancy. The fetal central nervous system is relatively impermeable to T3 and the majority of fetal T3 present in the central nervous system during pregnancy is derived locally from maternal T4 actively transported into the intervillous space.⁴⁸ Treatment with liothyronine or desiccated thyroid leads to a relative excess of T3 and relatively low concentrations of T4, which could lower fetal central nervous system T4 and T3 availability.^{48,153,154} Therefore, women using

liothyronine or desiccated thyroid preparations should be recommended to switch to LT4 monotherapy to avoid insufficient thyroid hormone availability for the fetal brain. For switching from combination T3 and T4 therapy to LT4 monotherapy, every 5 mcg of liothyronine may be considered equivalent to 20 mcg LT4. For switching from desiccated thyroid extract to LT4 monotherapy, every 60 mg grain of desiccated thyroid may be considered equivalent to 88 mcg LT4.¹⁵⁵

Gestational treatment and management. Recent studies showed that mild overt hypothyroidism during pregnancy only persists in less than half of all untreated women upon rechecking thyroid function tests after 1-3 weeks (especially if TSH is <6.0 mU/L), and the persistence is even lower when thyroid function tests are reassessed in the third trimester.^{51,52} This indicates that for mild overt hypothyroidism during pregnancy, reassessment can be considered before starting treatment. We defined "mild" overt hypothyroidism as a TSH that is elevated above the pregnancy upper limit but less than 6 mU/L based on the possibility of normalizing upon reassessment, low risk of adverse pregnancy outcomes, and expert opinion.^{33,51,52,146} This recommendation is conditional upon patient preference. A clinical example for this would be if a patient with mild overt hypothyroidism during pregnancy is doubtful or anxious about starting LT4 after counseling on the presumed (minor) risks of remaining untreated or delayed treatment.

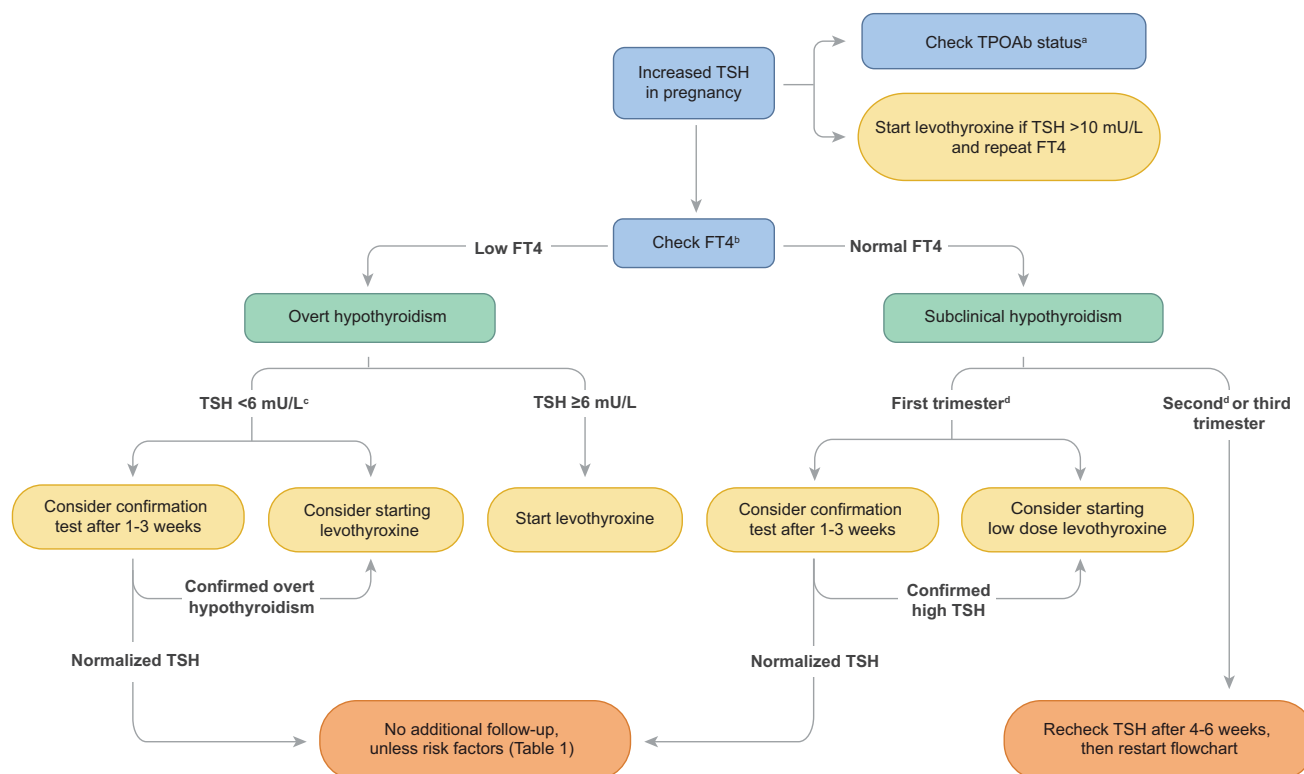
In contrast, overt hypothyroidism with a TSH equal to or above 6 mU/L during pregnancy is an indication for LT4 treatment. LT4 doses for newly diagnosed overt hypothyroidism in pregnancy may be estimated with the guidance used for full replacement (1.5-1.7 mcg/kg/day) plus an additional 20-30% dose increase required for gestation.



FLOWCHART 1. Approach to increased TSH levels in preconception. Green boxes indicate a diagnosis, yellow boxes indicate an action, and orange boxes indicate recommended follow-up. ^aWomen with a high TSH have a higher risk of TPOAb positivity. TPOAb positivity is associated with a 7–9% risk of developing subclinical hypothyroidism preconception or during pregnancy. TPOAb status can guide screening in a future pregnancy and aid in counseling for postpartum thyroiditis risk. Euthyroid TPOAb positivity is not an indication for levothyroxine (refer to *Recommendations Table 7*). ^bOr alternatives as described in the thyroid function testing subsection of this guideline. ^cFor example, when fertility is already planned or when the chance of a successful pregnancy due to age or comorbidities would be further limited by postponing treatment. ^dBased on expert opinion, this could be defined, for example, as a TSH concentration >6 mU/L or in case of subclinical hypothyroidism with concomitant TPOAb positivity.

The majority of women using LT4 for overt hypothyroidism will require a dose increase of approximately 25% by week 12 and approximately 50% by week 20 to remain euthyroid.^{156–158} To reach a steady state, the dose can be increased upon a positive pregnancy test and titrated thereafter, either by increasing the daily dose or by increasing the dose by two LT4 daily dosages per week. If all women undergo a standardized dose increase, there is a slightly

higher risk of overtreatment in women with a prepregnancy TSH <1.5 mU/L, women with a prepregnancy LT4 dose >100 mcg/day, and women who increase the weekly dose by two tablets.^{156–158} Therefore, the preconception TSH and LT4 dose should be taken into account when considering a dose increase and/or the quantity of that increase. At delivery, the LT4 dose can be changed back to the prepregnancy dose, and thyroid function can be tested after six weeks.



FLOWCHART 2. Approach to increased TSH levels in pregnancy. Green boxes indicate a diagnosis, yellow boxes indicate an action, and orange boxes indicate recommended follow-up. ^aWomen with a high TSH have a higher risk of TPOAb positivity. TPOAb positivity can be used for counseling on postpartum thyroiditis and guide screening in future pregnancies. ^bOr alternatives as described in the thyroid function testing subsection of this guideline. ^cFor mild forms of overt hypothyroidism, the risk profile and chance of TSH normalization are similar to those of subclinical hypothyroidism. Therefore, confirmatory testing can be considered using a shared decision-making approach. ^dThe distinction between the first and second trimester remains arbitrary, and management can be altered if the gestational age is within reasonable proximity on a case-by-case approach.

Subclinical hypothyroidism in preconception and pregnancy

Recommendations Table 10: Subclinical Hypothyroidism Preconception and in Pregnancy	Strength*	Level #
Profound maternal subclinical hypothyroidism (i.e. a TSH >10 mU/L) during pregnancy should be treated with levothyroxine.	Good Practice Statement	
For mild maternal subclinical hypothyroidism diagnosed in the first trimester, ^a levothyroxine treatment may be considered.	Conditional	Low
For mild maternal subclinical hypothyroidism diagnosed after the first trimester, ^a levothyroxine treatment should not be offered and follow-up TSH testing can be performed after 4-6 weeks.	Strong	High
For maternal subclinical hypothyroidism treated with levothyroxine, TSH may be checked every 4 weeks until midgestation and at least once around 30 weeks gestation.	Conditional	Low
For women using levothyroxine prior to or during pregnancy, a TSH within the normal range but below 2.5 mU/L may be targeted.	Conditional	Low

^a Trimester cut-offs are pragmatically defined and do not reflect thyroid-related physiology. Therefore, it is reasonable to adjust this cut-off by several weeks on a case-by-case basis.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TSH, thyroid stimulating hormone

In women known to have subclinical hypothyroidism prior to pregnancy, there is a lower threshold to start LT4 treatment during preconception or early gestation as compared with subclinical hypothyroidism in nonpregnant populations. A carefully balanced diagnostic, counseling, and

treatment strategy is required to optimize potential LT4 benefits while preventing potential harms related to overtreatment and patient anxiety. For this topic, there is abundant low-to-moderate quality evidence but only sparse high-quality evidence to support recommendations. The main

foundations of the available evidence are three randomized trials that investigated LT4 for subclinical hypothyroidism during pregnancy. The task force has assessed subanalyses and between-study comparisons from the randomized trials, often supported by observational studies, to form recommendations for this subsection.

Epidemiology and physiology. The prevalence of subclinical hypothyroidism is approximately 2.4–6.0% in women of childbearing age,^{101,120} and subclinical hypothyroidism during pregnancy occurs in approximately 3.2–3.5% of all pregnant women,^{57,110} although the prevalence during pregnancy largely depends on the upper limit used for TSH (laboratory-specific vs. a fixed limit).^{38,57,110} The main risk factor for hypothyroidism before or during pregnancy is thyroid autoimmunity.^{38,108} Greater age is associated with a higher risk of subclinical hypothyroidism preconception and during pregnancy, and considerable regional and interpopulation differences in subclinical hypothyroidism prevalence occur.^{38,101,107,110} It remains unknown what proportion of subclinical hypothyroidism during pregnancy is pre-existing disease identified for the first time during pregnancy versus gestation-specific subclinical hypothyroidism related to the increased thyroid hormone demand associated with pregnancy.

Clinical presentation and evaluation. The clinical presentation and evaluation of subclinical hypothyroidism outside of the perinatal period are summarized in detail elsewhere.¹¹¹ The majority of women diagnosed with subclinical hypothyroidism during pregnancy are identified when presenting for general obstetric care and have no hypothyroid symptoms.^{57,140,141} Assessing risk factors for iodine deficiency and checking TPOAb status is useful for etiological, therapeutic, and prognostic purposes as well as assessing the frequency of any follow-up during the remainder of pregnancy or in future pregnancies. Untreated subclinical hypothyroidism is associated with a higher risk of miscarriage, pre-eclampsia, placental abruption, preterm birth, and small for gestational age.^{33,34,159–161} The absolute risk difference for these pregnancy complications as compared with euthyroidism ranges between +1 to +5%.^{33,34,159–161} Within the group of women with subclinical hypothyroidism during pregnancy, a higher TSH concentration, earlier gestation at diagnosis, and TPOAb positivity are not associated with a clinically relevant higher risk of adverse outcomes.^{33,34,159–162} Therefore, although untreated subclinical hypothyroidism is associated with only small absolute increases in adverse pregnancy and child outcomes, this does not preclude consideration of LT4 treatment in selected circumstances. In these settings, treatment decisions are driven primarily by timing of diagnosis (preconception or early gestation), risk of progression during pregnancy, and patient values and preferences, rather than by a large anticipated reduction in absolute risk.

Treatment and management. The management of subclinical hypothyroidism outside of the perinatal period is summarized in detail elsewhere,¹¹¹ and recommendations for women with infertility can be found in Section E. For women with subclinical hypothyroidism who are planning pregnancy, postponing pregnancy and repeating thyroid

function tests after four to six weeks before attempting pregnancy should be preferred, rather than immediate LT4 treatment, given that thyroid function tests will normalize for a large number of women. If subclinical hypothyroidism persists upon retesting, or if a 6- to 12-week waiting period is not feasible, then LT4 treatment can be started at a low dose (e.g., 50 mcg/day). A logical LT4 treatment target for a woman with a wish to conceive is a TSH in the reference interval to ensure adequate thyroid hormone availability, but below 2.5 mU/L to create a margin of safety for remaining euthyroid in anticipation of a state of increased thyroid hormone demand during pregnancy. Women using liothyronine or desiccated thyroid preparations should be advised to switch to LT4 monotherapy to avoid insufficient thyroid hormone availability for the fetal brain (see subsection on overt hypothyroidism in pregnancy).⁴⁸

Limited data from one small, randomized trial and several observational studies support the concept that LT4 treatment for subclinical hypothyroidism diagnosed during the first trimester can be beneficial. In an Iranian randomized trial that treated the highest proportion of patients in the first trimester (62% and 52% in TPOAb-positive and TPOAb-negative women, respectively), LT4 treatment was associated with a lower rate of preterm birth compared with no treatment (5.3% vs. 24.9% in TPOAb-positive women; 7.3% vs. 19% in TPOAb-negative women). In this trial, there was also a higher median offspring gross motor development score (60 vs. 57.5 points on the Ages and Stages Questionnaire) but no corresponding effects on other neurocognitive domains at age 3 years.^{137,163,164} Notably, the positive results were only obtained if subclinical hypothyroidism was defined using a TSH cutoff of >4.0 mU/L, but there was no LT4 benefit if subclinical hypothyroidism was defined using a TSH of >2.5 or >3.0 mU/L. In a large trial performed in the United Kingdom and Italy (Controlled Antenatal Thyroid Screening [CATS] trial), high-dose LT4 (150 mcg/day) started at a median 12 weeks' and 3 days' gestation did not improve obstetric outcomes (personal communication with authors) or offspring IQ at age 3 years.¹⁶⁵ In a large US National Institutes of Health trial, LT4 treatment started on average at 17 weeks' gestation did not improve obstetric outcomes or offspring IQ at age 5, and LT4 effects did not meaningfully differ according to the timing of treatment initiation (before or after 17 weeks).¹⁶⁶ The concept that the first trimester is a more opportune period for LT4 treatment benefits as compared with later stages of pregnancy is supported by some observational studies investigating miscarriage and offspring IQ or brain morphology,^{35,159,167} but not by studies investigating other outcomes, such as preterm birth.³³ Trimesters are pragmatically defined and do not reflect thyroid-related physiology; therefore, it is reasonable to adjust these trimester-specific recommendations in this guideline by several weeks on a case-by-case basis (example scenarios: delayed diagnosis due to late entry into prenatal care; an initial or follow-up abnormal TSH result shortly after the end of the first trimester rising TSH concentration or progression toward overt hypothyroidism shortly after 12 weeks' gestation).

For starting LT4 in women with subclinical hypothyroidism during the first trimester, we advise a shared-decision-making approach that includes counseling on the potential

risks of untreated subclinical hypothyroidism and the lack of conclusive evidence for the benefits of LT4 treatment, as summarized in Flowchart 2. Furthermore, recent studies showed that subclinical hypothyroidism during pregnancy only persists in 41% of all untreated women upon rechecking thyroid function tests after about 3 weeks (especially if TSH is <6.0 mU/L), and in 25% when thyroid function tests are reassessed in the third trimester.^{51,52} This indicates that reassessment can be considered before starting treatment. A clinical example for this would be if a patient with subclinical hypothyroidism during pregnancy is doubtful or anxious about starting LT4 after counseling on the presumed risks of remaining untreated or delayed treatment. When the decision is made to defer LT4, repeat thyroid function testing can be performed within three weeks to exclude progression to overt hypothyroidism. When the decision is made to start LT4 therapy, the optimal dose is one that is high enough to normalize TSH but low enough to prevent potential overtreatment. The concept of potential harm related to LT4 overtreatment and the recommendation to start with 25–75 mcg/day depending on the TSH concentration and weight of the patient are based on data from randomized trials and per-

LT4 150 mcg/day) had children with more symptoms of attention-deficit/hyperactivity disorder and behavioral difficulties but similar anthropometric, metabolic, and neurocognitive outcomes.^{168–170} Similar to the management of overt hypothyroidism during pregnancy, a treatment target of TSH in the reference interval, but below 2.5 mU/L to create a safety margin for undertreatment, can be used. In contrast to overt hypothyroidism, for subclinical hypothyroidism diagnosed preconception, there are no data to support a standard 25% LT4 dose increase upon a positive pregnancy test. Based on the personal experience of the writing group, either a small dose increase (e.g., 12.5 mcg/day) or a reflex dose change based on thyroid function testing every 4 weeks during the first half of pregnancy, both yield satisfactory results. After delivery, an LT4 cessation trial should be strived for to prevent unnecessary chronic LT4 use. A shared decision on the cessation trial itself and also its timing can be made taking into account the TSH at diagnosis, TPOAb status, breastfeeding, and future pregnancy planning, while noting that the benefit of LT4 on breastfeeding outcomes is based on very limited data.

Thyroid autoimmunity in preconception and pregnancy

Recommendations Table 11: Thyroid Autoimmunity Preconception and in Pregnancy		Strength*	Level #
For euthyroid TPOAb and/or TgAb positive pregnant women, levothyroxine treatment should not be offered.		Strong	High
For euthyroid TPOAb and/or TgAb positive pregnant women, do not offer selenium supplementation.		Conditional	Moderate
For euthyroid TPOAb and/or TgAb positive pregnant women, do not offer glucocorticoids or intravenous immunoglobulin treatment.		Conditional	Low

See Recommendations Table 1 for guidance on follow-up thyroid function testing

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TPOAb, thyroperoxidase antibody; TgAb, thyroglobulin antibody

Dissenting comments for Recommendations Table 11 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

sonal experiences of the writing group.^{35,100,105,106,168–172} For example, women who were included in the CATS trial and showed biochemical or clinical signs of overtreatment (using

This section focuses on TPOAb positivity; considerations on TgAb positivity can be found in Box 4. Autoimmune hyperthyroidism is discussed below in Section G. The

Box 4. Perinatal TgAb positivity and other signs of thyroid autoimmunity

TgAb positivity is a reflection of thyroid autoimmunity and a risk factor for overt hypothyroidism during pregnancy.⁵⁷ However, TgAb positivity has less diagnostic accuracy for hypothyroidism than TPOAb positivity.^{183,184} Furthermore, as compared to (euthyroid) TPOAb positivity, it is less likely that (euthyroid) TgAb positivity is a risk factor for miscarriage or preterm birth.^{33,133,136,185} For these reasons, there are more studies available on TPOAb positivity, and TPOAb positivity remains the primary thyroid antibody to be checked for etiological or prognostic purposes both in pregnant and non-pregnant individuals. Some studies in non-pregnant individuals have suggested that thyroid sonography can identify individuals with thyroid antibody negative thyroid autoimmunity. However, the lack of data in the perinatal period limits the usefulness of ultrasound for detecting thyroid autoimmunity. Moreover, if the indication for a thyroid ultrasound is unclear, the risks of diagnosing thyroid nodules or small (i.e. not clinically meaningful) thyroid cancers, which might result in additional testing or treatment, is more likely to outweigh any benefits.

- There is no indication for routine perinatal TgAb measurements.
- If a woman is known to have isolated TgAb positivity or previous incidental signs of thyroid autoimmunity on ultrasound when entering the perinatal period, it is sensible to approach thyroid management similar to the recommendations for TPOAb positive women.
- A small subgroup in which additional TgAb measurement could be considered for the purpose of identifying an indication for preconception or gestational thyroid function screening would be a euthyroid TPOAb negative woman with a high risk of thyroid autoimmunity (for example: previous thyroiditis, concomitant autoimmune disease, first degree relative with thyroid autoimmunity) and a high-normal TSH.

TgAb, thyroglobulin antibody; TPOAb, thyroperoxidase antibody; TSH, thyroid stimulating hormone

interpretation of TPOAb positivity in the perinatal period is similar to that outside of pregnancy, in the sense that euthyroid TPOAb positivity should be considered a risk factor for thyroid disease rather than a disease entity in itself. However, increased thyroid hormone demand makes pregnancy a window of increased risk of new onset, or progression of, hypothyroidism in women with thyroid autoimmunity, thus warranting active screening and follow-up. Recommendations in this subsection are based on a large body of prospective cohort studies and multiple randomized trials.

Epidemiology and physiology. The prevalence of TPOAb positivity in women of childbearing age and pregnant women ranges between 5% and 15% (worldwide average 9%).^{57,101,102} Risk factors for TPOAb positivity have poor discriminative ability and include other autoimmune diseases, a first-degree relative with thyroid autoimmunity, greater age, obesity, and nulliparity; in addition, ethnic differences also exist.^{101,102,132} Thyroid autoimmunity can reduce the functional capacity of the thyroid gland, which can become apparent during pregnancy as thyroidal stimulation by hCG is impaired in the majority of TPOAb-positive women.^{22,23,25} In line with this physiology, TPOAb positivity is the most important risk factor for hypothyroidism during pregnancy. Of all TPOAb-positive women, 4% have overt hypothyroidism and 18% have subclinical hypothyroidism during pregnancy (as compared with 0.4% and 3.2% for TPOAb-negative women, respectively).⁵⁷ As pregnancy progresses, TPOAb concentrations can decrease by 60% due to gestational immunotolerance,²⁵ and this can change the TPOAb status from positive during early pregnancy to negative during the third trimester in up to 16% of cases.^{51,52} Furthermore, women with a TPOAb concentration just below the positivity cutoff have slightly higher TSH and

There are no known factors that modify these risks in euthyroid TPOAb-positive women.

Treatment and management. Since publication of the previous version of these guidelines, three randomized trials have shown that for women with euthyroid TPOAb positivity, LT4 therapy started either preconception^{100,105,106} or in early pregnancy¹³⁷ does not improve adverse obstetric or newborn outcomes. We extrapolated these negative results, obtained in a high-risk population (a large proportion of women had infertility or a previous miscarriage), to also make recommendations that include the general population. There were no factors that modified the response to LT4 treatment, including a TSH >2.5 mU/L, previous miscarriage(s), maternal age, or the TPOAb concentration.^{100,105,106,135,137,138} Thus, the slightly higher risks of adverse pregnancy outcomes (especially miscarriage and preterm birth) in TPOAb-positive women do not seem to be modified by LT4 treatment. Since this also suggests that the mechanism underlying the higher risk for TPOAb-positive women is not related to changes in thyroid hormone availability, the underlying mechanism remains to be elucidated. It is plausible that thyroid antibodies are a reflection of a more general susceptibility to autoimmunity and that other autoimmune processes are underlying the higher risks of pregnancy complications.¹³⁹ However, there are currently no data to support a dietary intervention or the use of immune-system-altering medications such as glucocorticoids, intravenous immunoglobulins, or selenium to improve obstetric outcomes or risk for (gestational) hypothyroidism.^{174–180}

Isolated hypothyroxinemia in preconception and pregnancy

Recommendations Table 12: Isolated Hypothyroxinemia Preconception and in Pregnancy		Strength*	Level #
For maternal isolated hypothyroxinemia diagnosed in the first trimester, do not offer levothyroxine treatment.		Conditional	Low
For maternal isolated hypothyroxinemia diagnosed after the first trimester, levothyroxine treatment should not be offered.		Strong	High

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

Dissenting comments for Recommendations Table 12 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

lower fT4 concentrations during pregnancy, as compared with women with TPOAb concentrations below the 80th percentile.¹⁷³ Therefore, when the initial titer of TPOAb status is in the high-normal range of the reference interval during pregnancy, follow-up of thyroid function tests similar to what is advised for TPOAb-positive women can be considered.

Clinical presentation and evaluation. The clinical presentation and evaluation of TPOAb positivity during the perinatal period are related to hypothyroidism and similar to those outside of the perinatal period, which is summarized in detail elsewhere.¹¹¹ Pregnant women with euthyroid TPOAb positivity do not present with symptoms, but have a higher risk of miscarriage and preterm birth.^{33,100,105,106,133,140,141} The absolute risk difference as compared with TPOAb-negative women ranges from about +2% to +8% for miscarriage, and about +2 to +3% for preterm birth.^{33,105,134–136}

Isolated hypothyroxinemia is predominantly a pregnancy-specific thyroid function test abnormality with an unclear etiology. Recommendations in this subsection are based on a large body of prospective cohort studies and two randomized trials.

Epidemiology and physiology. The prevalence of isolated hypothyroxinemia in women of childbearing age is about 0.2% and ranges between 2.0% and 2.2% in pregnant women.^{57,101,110} The prevalence is higher when laboratory and pregnancy-specific reference intervals are used in the first trimester (0.75% vs. 2.1%), but similar across definitions in the second trimester.³⁸ The etiology of isolated hypothyroxinemia is not clear, but risk factors include iodine deficiency, iron deficiency, higher BMI, greater age, twin pregnancy, exposure to endocrine disruptors, and angiogenic factors,^{57,184} but not TPOAb positivity.¹⁸⁵ Furthermore, it

can also be attributed to changes in fT4 assay performance during pregnancy, leading to falsely low fT4 concentrations in some women.¹⁸⁴

Clinical presentation and evaluation. During pregnancy, most women diagnosed with isolated hypothyroxinemia are identified when presenting for general obstetric care. While isolated hypothyroxinemia is associated with more hypothyroid symptoms than euthyroidism, this difference is not large enough to distinguish these two biochemical states clinically.^{140,141} Isolated hypothyroxinemia is associated with a higher risk of premature rupture of membranes, gestational diabetes mellitus, (very) preterm birth, large for gestational age, and a lower offspring IQ.^{33,34,186–189} The absolute risk difference, as compared with euthyroid women, ranges from about +2% to +4% for obstetric outcomes and an average of two to four points lower offspring IQ.^{33,105,134–136} There are no known factors that modify these risks in women with isolated hypothyroxinemia. The differential diagnosis for isolated hypothyroxinemia may include central hypothyroidism, and screening for symptoms of deficiency or excess of pituitary hormones and/or apoplexy/hypophysitis may be considered. However, central hypothyroidism has a very low incidence, especially in patients lacking risk factors or related symptoms. Therefore, in the absence of central hypothyroidism risk factors (such as a history of previous hypothalamic or [infiltrating] pituitary disease or cranial irradiation) or symptomatology, no further routine diagnostics seem warranted.

Treatment and management. Two randomized trials showed that for women with isolated hypothyroxinemia, LT4 therapy started in the second trimester does not improve obstetric or offspring neurocognitive outcomes, regardless of TPOAb status or iodine intake.^{165,166,169,170,190} There are no data from randomized trials on early pregnancy LT4 treatment for isolated hypothyroxinemia. Isolated hypothyroxinemia in early

G. Hyperthyroidism Preconception, In Pregnancy, and Postpartum

The diagnostic approach and management of thyrotoxicosis in women during preconception, pregnancy, and lactation requires careful consideration and a management plan tailored to the individual patient. The most relevant considerations relate to the goal of restoring euthyroidism as quickly as possible, while mitigating the risks of treatment during this vulnerable period. In addition, the unique overlap of clinical signs, symptoms, and laboratory tests with physiological alterations of thyroid parameters during gestation can be challenging in the care of the pregnant hyperthyroid woman.

What is new in this guideline: (1) In the rare case of a pregnant patient who requires urgent thyroid surgery, this operation should be performed at the time required. While new anesthesia recommendations published since the previous iteration of these guidelines endorse that surgery requiring general anesthesia can be performed safely during any trimester, it is still best to proceed with such surgery in the second trimester if possible. First-trimester miscarriages may be incorrectly ascribed to surgery (as miscarriage rates are high in the first trimester), and fetal monitoring is warranted during surgery in the third trimester when the fetus is postviability and there may be a risk of needing an urgent delivery. (2) There is greater emphasis on the usefulness of serum TSH receptor antibodies (TRAb) and/or thyroid-stimulating immunoglobulin (TSI) titers (both their absolute values and the duration of their elevation) in guiding when ATDs may be discontinued to provide the lowest chance of Graves' disease relapse, which can be used in shared decision-making during preconception counseling.

Epidemiology and physiology

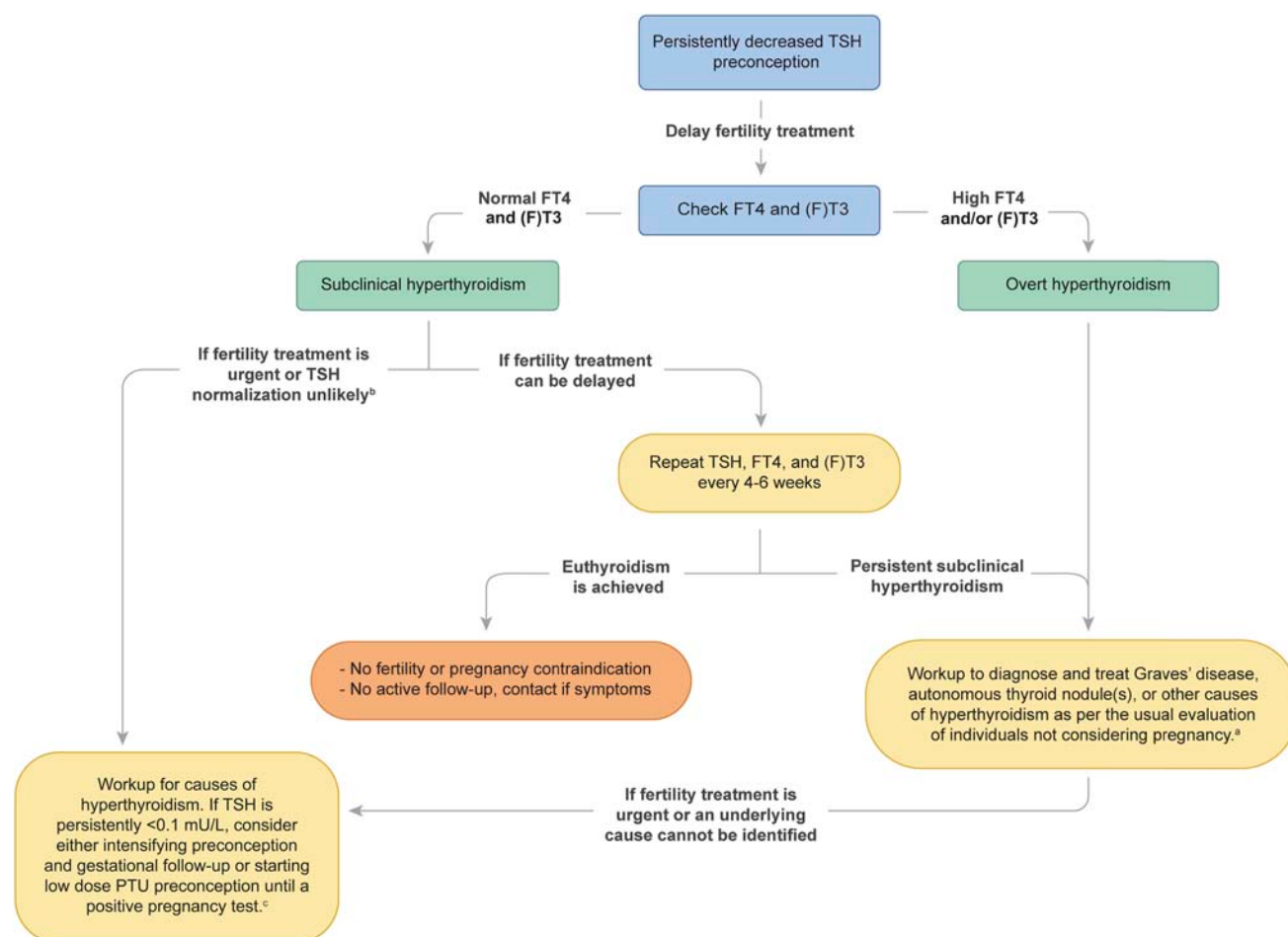
Recommendations Table 13: Evaluation of Hyperthyroidism in Pregnancy		Strength*	Level #
Thyroid function testing should not be pursued in pregnant women with hyperemesis gravidarum if there are no other clinical signs of hyperthyroidism ^a .		Good Practice Statement	
Thyroid ultrasonography is not suggested as a method to distinguish GTT from Graves' disease in pregnant women.		Conditional	Low
Isotope scanning is contraindicated in pregnancy and should not be used in the diagnostic evaluation of hyperthyroidism.		Good Practice Statement	

^a Predominantly palpitations that persist after rehydration and antiemetics. If palpitations are caused by GTT, these can be treated symptomatically with propranolol.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
GTT, gestational transient thyrotoxicosis

pregnancy persists upon reassessment in only 18% of cases.^{51,52} Follow-up thyroid function testing after two to six weeks can be considered for isolated hypothyroxinemia diagnosed around the first trimester to exclude progression to hypothyroidism, as early isolated hypothyroxinemia is less likely to be related to fT4 assay interference or fT4 reference interval definitions compared with later pregnancy. Because iron and/or iodine deficiency are risk factors for isolated hypothyroxinemia, it is reasonable to assess iron status and risk factors for iodine deficiency in women with isolated hypothyroxinemia.

A suppressed serum TSH concentration is frequently encountered in early gestation, when the hCG concentration rapidly increases through placental production. Gestational transient thyrotoxicosis (GTT) is the physiological condition resulting from the weak thyroid-stimulating effect of hCG on TSH receptors, typically manifesting as a suppressed TSH and mildly increased fT4 concentrations. Upon the presentation of biochemical hyperthyroidism in pregnancy, GTT should be distinguished from other less common hyperthyroidism etiologies, including (new onset or recurrent) Graves' disease. Other etiologies of thyrotoxicosis in

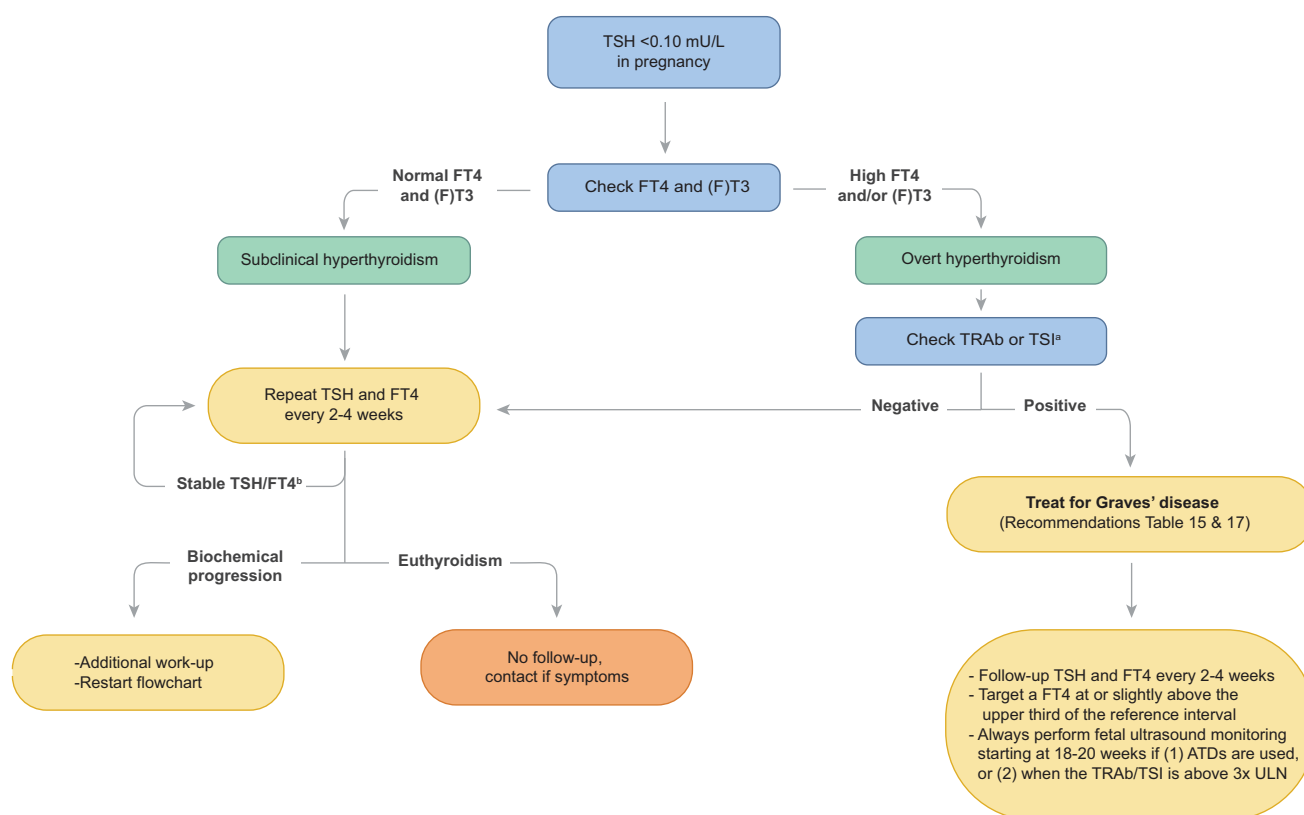


FLOWCHART 3. Approach to decreased TSH levels in preconception. Green boxes indicate a diagnosis, yellow boxes indicate an action, and orange boxes indicate recommended follow-up. ^aIdeally, the treatment for the etiology of hyperthyroidism should be completed and euthyroidism restored (confirmed by two TSH concentrations in the reference range at least six weeks apart) before fertility treatment begins. ^bFor example, if the TSH has been persistently <0.1 mU/L. ^cRefer to “Subclinical and Overt Hyperthyroidism in Infertility” in Section E.

TABLE 2. DISTINGUISHING BETWEEN GESTATIONAL TRANSIENT THYROTOXICOSIS (GTT) AND GRAVES’ DISEASE

Feature	GTT	Graves’ Disease
Symptoms of thyrotoxicosis before pregnancy	None	Often
Symptoms of hyperemesis gravidarum (nausea/vomiting)	Often	Usually not present
Personal or family history of thyroid disease	Usually absent	Often present
Presence of goiter	None/low	May be present as diffuse goiter
Signs of thyroid eye disease	None	May be present
Serum FT3 concentration (Box 6)	Usually normal or mildly raised	Raised
Serum TRAb and/or TSI concentration	Normal	Raised
Serum TT3 (ng/dL)/TT4 (mcg/dL) ratio ³²⁹	Typically <20	Typically >20
Serum TSH concentration	Usually normalizes by the third trimester of pregnancy	Often suppressed throughout pregnancy

GTT, gestational transient thyrotoxicosis; FT3, free triiodothyronine; TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone



FLOWCHART 4. Approach to decreased TSH levels in pregnancy. Green boxes indicate a diagnosis, yellow boxes indicate an action, and orange boxes indicate recommended follow-up. (f)T3 = serum free and/or total T3 (see Box 5 in these guidelines). ^aFor women with a clear presentation of hCG-induced hyperthyroidism/gestational transient thyrotoxicosis (e.g., with a nonfully suppressed TSH, twin pregnancy, or hyperemesis gravidarum without extrathyroidal signs of Graves' disease), it is reasonable to follow up with a TSH and fT4 in two to four weeks before checking TRAb and/or TSI. ^bAssess for a palpable thyroid nodule. If present, then follow biochemical progression and consider ATDs depending on the severity of hyperthyroidism. For example, repeat TRAb and/or TSI, (f)T3 measurement, thyroid ultrasound, and postpartum diagnostic imaging. TSI, thyroid-stimulating immunoglobulin.

pregnant women are exceedingly rare and include toxic multinodular goiter and toxic adenoma, the thyrotoxic phases of subacute painful or painless thyroiditis, TSH-secreting pituitary adenoma, struma ovarii, functional thyroid cancer metastases, and germline TSH receptor mutations that are hypersensitive to hCG.¹⁹¹ Thyrotoxicosis can also result from overtreatment with thyroid hormone replacement or the intentional or unintentional intake of thyroid hormone.¹⁹²

The prevalence of GTT varies widely, due to the heterogeneity in the definition of GTT, overlap with other reasons for a suppressed TSH in pregnancy, and the inclusion of women with hyperemesis gravidarum in some studies.^{8,193,194} It is estimated that the general prevalence of GTT ranges from <1% to 11% during pregnancy,¹⁹⁵ depending on the geographic region. GTT occurs in up to 66% of women with hyperemesis gravidarum.¹⁹⁶ Data on mild hyperthyroidism (usually due to GTT) during pregnancy are reassuring, as it is not associated with higher risks of adverse pregnancy or birth outcomes, such as preeclampsia, gestational hypertension, preterm birth, and small for gestational age.^{34,160,197,198}

Graves' disease is the most common cause of nonphysiological, pathological thyrotoxicosis in women of childbearing age, occurring in approximately 0.4% of women during preconception and 0.2% during pregnancy.¹⁹⁹ Autonomous

thyroid nodules (ATNs), including multinodular goiter, have an estimated yearly incidence of 1–18 per 100,000 among nonpregnant women aged 20–39 years,^{200,201} while the prevalence of coexisting ATNs and Graves' disease (termed the Marine–Lenhart syndrome) in nonpregnant individuals was 0.26% in a study from Japan, an overall iodine-sufficient region.²⁰²

Clinical presentation and evaluation

Women may come to attention during preconception and pregnancy for abnormal thyroid function tests checked in response to hyperthyroid symptoms or during routine prenatal care. Guidance for the evaluation of a decreased TSH in women planning pregnancy is summarized in Flowchart 3. Hyperthyroidism found during preconception should generally be evaluated and treated in the same way as in individuals not planning pregnancy,²⁰³ with the added consideration of fertility treatment if applicable.

The evaluation of hyperthyroidism in a pregnant woman presents distinct challenges. It is important to distinguish Graves' disease in pregnancy from other causes (Table 2). GTT is more common in states associated with

Box 5. Considerations of (F)T3 testing in gestational hyperthyroidism

In the case of suspected hyperthyroidism in pregnancy, several pertinent issues should be noted when considering the measurement of serum (F)T3.

- Analytic concerns of the free thyroid hormone assays in pregnancy, particularly for FT3, may limit their usefulness (Section C). Compared to total T3, FT3 is not altered by binding proteins and appears to be more stable throughout pregnancy^{12,207}, although FT3 may be not as widely available as total T3. When T3 estimates are needed, it is reasonable to apply the same considerations as described for free and total T4 in Section C, while noting the general limitations of the FT3 assay similar to its concerns in nonpregnant individuals.
- In general, serum (F)T3 testing can be performed in cases of a suppressed TSH and normal FT4, to distinguish subclinical hyperthyroidism from overt hyperthyroidism, especially if this would change management.²⁰⁸
- If T3 thyrotoxicosis is suspected, for example hyperthyroidism caused by Graves' disease or a T3-producing thyroid nodule, T3 testing may be considered in a pregnant woman with a normal FT4 and a TSH <0.01 mU/L, or TSH ranging from >0.01 to <0.3 mU/L in the presence of thyrotoxic symptoms, thyroid eye disease, a palpable thyroid nodule, and absent use of ATDs or thyroid hormone medication.²⁰⁸

In general, serum T3 testing may be helpful to initially distinguish the etiology of hyperthyroidism during pregnancy and can be used to guide the diagnosis between GTT, Graves' disease (Table 2), and a T3-producing thyroid nodule. However, maternal T3 concentrations are not associated with fetal T3 or (F)T4, and as such, targeting a normal (F)T3 during pregnancy can cause fetal hypothyroidism.²⁰⁹ Therefore, (F)T3 should not be used to monitor or inform medical management for GTT or Graves' disease during pregnancy.²⁰⁹

FT3, free triiodothyronine; T3, triiodothyronine; TSH, thyroid stimulating hormone; FT4, free thyroxine; ATD, antithyroid drug; GTT, gestational transient thyrotoxicosis

high hCG concentrations, such as early pregnancy, hyperemesis gravidarum,¹⁹⁶ and multiple gestation pregnancies.¹⁹⁸ In contrast, women with untreated Graves' disease during pregnancy would be expected to have persistently low TSH concentrations, persistently increased fT4 concentrations after the first trimester,²⁰⁴ and hyperthyroid symptoms that have often times been present before pregnancy. Positive serum TRAb and/or TSI titers, the presence of thyroid eye disease, and a family history of Graves' disease and/or personal or other family history of autoimmunity also support the diagnosis of Graves' disease. It should be noted that serum TRAb and TSI concentrations are used interchangeably in this text, as there are no data to show superiority or differences in the upper limit of normal clinical decision cutoffs between the two. In women with hyperemesis gravidarum and no other clinical signs of hyperthyroidism, the relatively frequent occurrence of GTT, as well as the likely absent need for symptom treatment, supports the general lack of benefit of routinely checking serum thyroid function.

Guidance for the evaluation of a decreased TSH in pregnant women without known thyroid disease is summarized in Flowchart 4. Pregnant women with suppressed TSH concentrations should initially have a fT4 concentration measured, followed by serum TRAb or TSI levels if the fT4 concentration is elevated. A (f)T3 measurement can be considered if the fT4 is normal and distinguishing subclinical hyperthyroidism from overt hyperthyroidism would change management, or to help distinguish the etiology of hyperthyroidism (Box 5 and

Table 2). A typical approach to a pregnant woman with a decreased TSH concentration and a concurrently normal fT4 and (f)T3 concentration (i.e., subclinical hyperthyroidism) is to repeat serum thyroid function every two to four weeks until the TSH normalizes (as most cases of GTT will). If subclinical hyperthyroidism persists into the third trimester or evolves into overt hyperthyroidism, additional follow-up and/or reconsideration of the hyperthyroidism diagnosis should be considered. Those with persistent overt hyperthyroidism, particularly after 20 weeks' gestation, should undergo TRAb and/or TSI testing, followed by treatment or ongoing monitoring as indicated. There is no role of thyroid ultrasonography as a method to distinguish GTT from Graves' disease in pregnant women owing to their similar thyroidal mechanism of action.

For women with preexisting ATNs who become pregnant, there is a lack of rigorous data regarding the patterns of thyroid function changes during gestation, but the physiologically greater thyroid hormone needs during pregnancy may result in gradual improvement of the hyperthyroidism, even potentially resulting in normal thyroid function tests as pregnancy progresses. Thyroid hormone production in individuals with ATNs depends on iodine availability, emphasizing the need to be cautious with excess iodine intake and exposure during pregnancy. It is not possible to confirm an ATN as the etiology of hyperthyroidism in pregnancy, given the inability to perform nuclear medicine uptake and scanning during this period. For the evaluation of hyperthyroidism in lactation, guidance regarding radiopharmaceutical use is found in Section I.

Preconception management of hyperthyroidism (Graves' disease)

Recommendations Table 14: Graves' Disease Preconception		Strength*	Level #
The desire for conception should be assessed in women of childbearing age who have new or existing hyperthyroidism.		Good Practice Statement	
The risks and benefits of treatment options for hyperthyroidism, their impacts on a future pregnancy, and desired timeline to conception should be discussed in women with existing hyperthyroidism who are planning pregnancy.		Good Practice Statement	
Women taking methimazole (MMI) should be switched to propylthiouracil (PTU) if they are planning pregnancy. ^a		Strong	Moderate

^a If PTU is not available or if there are contraindications (allergy), we recommend that women continue MMI while trying to conceive, along with a discussion on the pros and cons of stopping MMI upon a positive pregnancy test and the option to pursue definitive therapy prior to pregnancy.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

MMI, methimazole; PTU, propylthiouracil

Women of childbearing age with newly diagnosed hyperthyroidism should be assessed for their desire to conceive in the near future. About 20% of women with hyperthyroidism present with menstrual disturbances and hyperthyroidism is associated with reduced fertility, although thyrotoxic women remain ovulatory.⁹ In a hyperthyroid woman desiring pregnancy, regardless of the underlying cause, the biochemical goal is to restore and maintain euthyroidism (confirmed by at least two sets of normal thyroid function tests obtained at least six weeks apart) before attempting conception.

Small studies show that correction of hyperthyroidism improves fertility, although this may be related to the restoration of menstrual cycle regularity. There are no high-quality studies comparing the relative impact of specific treatment modalities for Graves' disease on fertility; one small prospective study describes the improvement of menstrual irregularity in hyperthyroid women upon ATD initiation.²⁰⁸ Our understanding of the risks and benefits of thyroid surgery and ¹³¹I treatment in Graves' disease on fertility is primarily derived from their use in women with a history of differentiated thyroid cancer (DTC) (also see Section H), with mostly reassuring findings for effects on ovarian reserve, transient amenorrhea, and pregnancy rates following these therapies.^{209–212} Although supporting data are limited, it is reasonable to expect that once euthyroid, fertility and fecundity for women with a history of treated Graves' disease are similar to those without a history of Graves' disease.

The management of hyperthyroidism due to Graves' disease during preconception presents unique considerations (Table 3). Options for treatment with ATDs, ¹³¹I therapy, or total thyroidectomy should be discussed through a shared decision-making process. The choice and timing of these management decisions should weigh the pros and cons of the treatment options on fertility, the health of a future pregnancy and the fetus, and general maternal health. Women who are already taking methimazole (MMI) should be advised to switch to PTU (if available) once they are actively trying to conceive.

If PTU is not available, the lowest effective dose of MMI can be used for the shortest duration possible. The relative risks of MMI and PTU during preconception and pregnancy are discussed below (subsection on ATDs).^{213–215} While being treated with an ATD, women should be instructed to contact their clinician immediately should they become pregnant.

Women with Graves' disease who are considering radioactive iodine (RAI) treatment before conception should be counseled that serum TRAb and/or TSI concentrations will likely increase after RAI administration, which is associated with an increased risk of fetal and neonatal hyperthyroidism.²¹³ In pregnancy, however, the risk of fetal and neonatal hyperthyroidism is negligible if the serum TRAb and/or TSI concentrations are <3-fold the upper limit of normal.^{213,216} Attempting pregnancy could be considered if preconception serum TRAb and/or TSI concentrations are <3× the upper limit of normal or slightly above this threshold as TRAb and/or concentrations are expected to further decline during pregnancy as a result of increased immune tolerance. However, no guidance can be provided on a specific, safe preconception TRAb, and/or TSI concentration cut-off, as the expected decrease of individual TRAb and/or TSI concentrations in pregnancy is difficult to predict. Women who receive preconception ¹³¹I treatment for Graves' disease should be advised to defer pregnancy for at least six months to minimize the potential adverse effects of radiation (as extrapolated from data on ¹³¹I treatment for DTC).²¹⁷

Finally, some women may elect to undergo total thyroidectomy for the definitive treatment of Graves' disease before pursuing pregnancy. Postoperative hypothyroidism should be managed with LT4 to ensure stable euthyroidism (confirmed by two consecutive normal thyroid function tests six weeks apart), along with attaining a TRAb and/or TSI concentration that minimizes the risk of fetal/neonatal hyperthyroidism before attempting to conceive.

TABLE 3. ADVANTAGES AND DISADVANTAGES OF TREATMENTS FOR PRECONCEPTION GRAVES' DISEASE

Graves' disease treatment option	Advantages related to pregnancy planning	Disadvantages related to pregnancy planning
ATDs continued in pregnancy	- Treatment is easy to take, discontinue or modify, and generally inexpensive - Usually the quickest option to achieve euthyroidism (achievable in majority of cases within 1-2 months) - Very low risk of permanent hypothyroidism - Relatively rapid decrease of TRAb and/or TSI concentrations	- Risk of congenital anomalies: +3% (PTU), +5% (MMI)²¹⁶⁻²¹⁷ - Overtreatment associated with fetal and neonatal hypothyroidism - Requires additional fetal ultrasounds during pregnancy - Risk of post-partum relapse (if stopped during pregnancy)
ATDs stopped upon pregnancy (Figure 5)	Discontinuation can be considered if there is a low risk of relapse (>6 months of treatment with ATD, normal TSH requiring <10 mg methimazole or <200 mg PTU per day, and TRAb concentrations <3x upper limit).	Risk of early pregnancy and post-partum relapse
I-131 therapy	- Non-invasive and definitive treatment option - Oral administration - Decreased goiter size usually seen	- Pregnancy contraindicated for at least 6 months - TRAb/TSI concentrations may increase transiently over the course of 1-3 years following I-131 administration, which may increase the risk of fetal and neonatal hyperthyroidism - Permanent maternal hypothyroidism is likely - Contraindicated in active moderate/severe thyroid eye disease - More than one dose may be needed
Total thyroidectomy	- Definitive treatment option - Euthyroidism usually easily achievable with thyroid hormone replacement within 1-2 months - Serum TRAb/TSI concentrations fall relatively quickly - Alleviates symptomatic goiter, if present	- Permanent hypothyroidism is guaranteed, requiring lifelong thyroid hormone replacement - Surgical risks, including recurrent laryngeal nerve injury (temporary ~7%, permanent <1%) and hypoparathyroidism (up to 6% permanent) - Recovery period

ATD, antithyroid drug; TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin; PTU, propylthiouracil; MMI, methimazole; TSH, thyroid stimulating hormone

Recommendations Table 15: Subclinical and Overt Hyperthyroidism in Pregnancy	Strength*	Level #
Subclinical hyperthyroidism or GTT should not be treated with ATD therapy, but propranolol may be used to ameliorate hyperthyroidism-related palpitations.	Strong	Moderate
In pregnant women with subclinical hyperthyroidism whose TSH concentration is <0.1 mU/L, serum thyroid function should be monitored without treatment every 2-4 weeks.	Good Practice Statement	
Overt hyperthyroidism that is not due to GTT (i.e. Graves' disease, autonomous thyroid nodule) should be treated, to minimize the duration of uncontrolled thyrotoxicosis in pregnancy.	Good Practice Statement	
Overt hyperthyroidism not due to GTT (i.e. Graves' disease, autonomous thyroid nodule) may be treated with ATD therapy, targeting a FT4 concentration at or slightly above the upper third of the reference interval. ^a	Conditional	Moderate

^a Because FT4 concentrations below this range are associated with a high risk of fetal hypothyroidism

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

GTT, gestational transient thyrotoxicosis; ATD, antithyroid drug; TSH, thyroid stimulating hormone; FT4, free thyroxine

Dissenting comments for Recommendations Table 15 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

Recommendations Table 16: Monitoring Graves' Disease in Pregnancy		Strength*	Level #
All pregnant women with a history of Graves' disease should have serum TSH, FT4, and TRAb and/or TSI measured in the first trimester.		Good Practice Statement	
For women with a history of Graves' disease who are not taking ATDs ^a and who have TRAb and/or TSI measured in the first trimester: A. If the TRAb and/or TSI concentration is >3 fold the upper limit of normal, TRAb and/or TSI measurements should be repeated at 18-22 and 30-34 weeks along with monitoring for signs of fetal hyperthyroidism (link to neonatal/fetal hyperthyroidism section). B. If the TRAb and/or TSI concentration at any time during pregnancy is <3 times the upper limit of normal and mother remains euthyroid, TRAb and/or TSI follow-up measurements and fetal hyperthyroidism monitoring should be stopped.		Strong	Moderate
Euthyroid women with a history of Graves' disease without prior definitive treatment and who have been in remission for >1 year should be monitored with thyroid function testing each trimester (Table 1), followed by maternal thyroid testing at 4-6 weeks and 4-6 months post-partum.		Good Practice Statement	

^a All women using ATDs require fetal thyroid ultrasound monitoring

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TSH, thyroid stimulating hormone; FT4, free thyroxine; TRAb, TSH receptor antibodies; TSI, thyroid stimulating hormone; ATD, antithyroid drug

Gestational management of GTT and Graves' disease

Subclinical hyperthyroidism in pregnant women generally does not require treatment, as the majority of such cases are attributable to GTT. Observational studies have not shown an association between untreated subclinical hyperthyroidism in pregnancy and adverse obstetric outcomes.^{33,34,160,187,218,219} GTT is typically self-limited and can be managed supportively with adequate hydration, control of hyperemesis if present, and alleviation of thyrotoxic symptoms with propranolol in the same routine doses as those used outside of pregnancy. ATD therapy should generally not be used for the treatment of subclinical hyperthyroidism. If GTT is particularly severe, low-dose PTU could be considered through shared decision-making and counseling about the harms and benefits of its use in pregnancy (see subsection below on ATD use in pregnancy).

For Graves' disease during pregnancy, the risks of obstetric and medical complications are related to the control of maternal hyperthyroidism and the duration of euthyroidism throughout gestation.^{222,223} Poor control of thyrotoxicosis caused by Graves' disease has been associated with pregnancy loss, pregnancy-induced hypertension, intrauterine growth restriction, stillbirth, seizure disorder among offspring,^{34,204,223-225} and thyroid storm and congestive heart failure in the mother during gestation.²²⁶ In women without Graves' disease, the association of hyperthyroidism in the first half of

pregnancy with adverse pregnancy outcomes is not consistent, and absolute risk differences are small.^{33,160,204,224,225,227-229} An important difference is that for Graves' disease, hyperthyroidism is likely more severe and lasts longer. Accordingly, women with Graves' disease who have overt hyperthyroidism at initial presentation or develop overt hyperthyroidism during pregnancy should be promptly treated, with the main goal to minimize the severity and duration of thyrotoxicosis.

Management options for Graves' disease in pregnancy (Table 4) include observation alone, ATD therapy, and total thyroidectomy in cases of uncontrollable hyperthyroidism or thyroid storm (Box 6). Limited data suggest that long-term use of saturated solution of potassium iodide (SSKI) may be an alternative option for the management of Graves' disease in iodine-sufficient populations, particularly if there is a higher risk or contraindications (i.e., allergies) to the usual therapies.^{96,213,230-232} Fetal thyroid ultrasound, fetal heart rate monitoring, and regular communication with the obstetrician or maternal-fetal medicine subspecialist are key for optimal risk assessment. The combination of persistently positive serum TRAb and/or TSI concentrations without a functioning maternal thyroid gland (such as after thyroidectomy and possibly after RAI therapy if it was administered preconception) can be particularly challenging and may require combined therapy with ATDs (to treat the fetus) and LT4 (to maintain maternal euthyroidism).

TABLE 4. RISKS AND GUIDANCE FOR TREATING GRAVES' DISEASE DURING PREGNANCY

Graves' disease treatment option	Risks	Guidance
ATDs	Congenital anomalies (more severe with MMI than PTU)	- Discuss ATD risks in pregnancy through shared decision-making in preconception. - Confirm pregnancy promptly if suspected. - Consider discontinuing ATDs in pregnant women at low risk of disease relapse during the first trimester. - If PTU is available, consider switching from MMI to PTU as soon as pregnancy is confirmed, using a dosing ratio of 1:20 (MMI to PTU). - If ATD use continues to be needed during pregnancy, treat with PTU (if available) until 16 weeks gestation. The choice for a preferred ATD after 16 weeks gestation is unknown.
	Fetal goiter	- Monitor maternal thyroid function every 2-4 weeks, aiming for FT4 concentration at or slightly above the upper third of the reference interval. - Fetal ultrasound monitoring should be performed monthly starting at 18-20 weeks gestation if the mother uses ATDs during pregnancy, monitoring frequency can be reduced for low dose ATD on a case-by-case basis. - If ATDs can be discontinued in pregnancy, then the maternal TRAb and/or TSI concentration can be checked^a and subsequent fetal ultrasound follow-up can be continued if the result remains >3 times the upper limit of normal after approximately 18-20 weeks gestation.
	Fetal and neonatal thyroid dysfunction	- Same guidance as for "Fetal goiter" above. - Consider discontinuing ATD treatment by 30-34 weeks gestation if appropriate.
Total thyroidectomy	Fetal and neonatal hyperthyroidism	Measure serum TRAb and/or TSI at time of surgery, and plan to repeat at 18-20 weeks and 30-34 weeks gestation if the result is >3 times upper limit of normal.
	Maternal thyroid storm and complications from anesthesia	Aim to achieve euthyroidism preoperatively, which likely requires ATD use and other therapies (such as potassium iodide, glucocorticoids, cholestyramine, plasmapheresis) if appropriate.
	Maternal hypothyroidism	Higher doses of thyroid hormone replacement are required for pregnancy. Patient should be closely monitored with serum thyroid function testing postoperatively.
	Surgical complications (hypoparathyroidism, RLN damage)	Refer to a high-volume surgeon.

^a Serum TRAb and/or TSI should initially be measured in the first trimester, and if elevated to >3 times the upper limit of normal, the measurement should be repeated at 18-22 weeks and 30-34 weeks gestation to guide need for a fetal ultrasound if the elevated TRAb and/or TSI concentration is sustained.

MMI, methimazole; PTU, propylthiouracil; ATD, antithyroid drug; FT4, free thyroxine; TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin; RLN, recurrent laryngeal nerve

Box 6. Management of uncontrollable hyperthyroidism and thyroid storm in pregnancy

For the treatment of decompensated hyperthyroidism during pregnancy, the same principles would apply as for other emergencies during pregnancy. For any therapeutic decision with a complex fetal/maternal trade-off, the health of the mother should be prioritized to safeguard maternal health and to optimize fetal outcomes considering their interconnected health status. Clinicians should consult with or refer patients to centers experienced in managing thyroid storm during pregnancy and closely collaborate with obstetricians and neonatologists.

- Propranolol should be the first beta-blocker of choice to be used to control maternal hyperadrenergic symptoms of hyperthyroidism, while closely monitoring the fetal risks of maternal beta-blockade.^{222,223}
- Thyroid surgery may be needed for severe cases. Although there are no data regarding the safety of SSKI therapy for the preparation for thyroidectomy in pregnancy and excess iodine is generally avoided in pregnancy (as iodide crosses the placenta [Figure 2], increasing the risk of neonatal goiter), short-term preoperative use or in the treatment of thyroid storm is unlikely to cause harm to the fetus. From limited data, long-term potassium iodide has been described as an alternative option for the management of Graves' disease in iodine sufficient populations, particularly if there is a higher risk or contraindications (i.e. allergies) to the usual therapies.^{96,215}
- Measurement of thyroid function tests may be performed approximately every 2 days to ensure a favorable trajectory. While optimal serum TSH and thyroid hormones concentrations are not well defined in this circumstance, failure of thyroid hormones to decrease and worsening clinical status could be considered indications to increase treatment doses and/or consider additional treatment options.

SSKI, saturated solution of potassium iodide

ATD treatment of Graves' disease in preconception and pregnancy

Recommendations Table 17: ATD Treatment of Graves' Disease Preconception and in Pregnancy	Strength*	Level #
Consider discontinuing ATD therapy for Graves' disease upon confirmed pregnancy if the woman is euthyroid on low dose ATD (MMI <5–10 mg/day or PTU <100–200 mg/day) taken for >6 months pre-pregnancy (Figure 4).	Conditional	Low
Following the discontinuation of ATD use in pregnancy, serum TSH, FT4 and clinical examination may be monitored every 1-2 weeks in the first trimester, then every 2-4 weeks in the second and third trimesters.	Conditional	Low
In pregnant women with a new diagnosis of Graves' hyperthyroidism or who have high risk of developing thyrotoxicosis if ATDs were to be discontinued, treatment with ATDs is advised as follows:		
Pregnant women with active Graves' disease managed with ATDs should have serum TSH, FT4, and TRAb and/or TSI concentrations measured as soon as pregnancy is confirmed and monitored with TSH and FT4 every 2-4 weeks thereafter.	Good Practice Statement	
PTU may be used if initiating ATD for the treatment of hyperthyroidism before 16 weeks of pregnancy.	Conditional	Low
If a woman is taking MMI during pregnancy, switching to PTU ^a may be considered until 16 weeks ^b depending on the time of presentation and MMI dose (see text).	Good Practice Statement	
If PTU is not available, MMI may be continued at the lowest effective dose for the shortest duration possible.	Conditional	Low
In case of thyrotoxicosis, propranolol may be used in routine dosages to ameliorate hyperthyroidism-related symptoms.	Good Practice Statement	

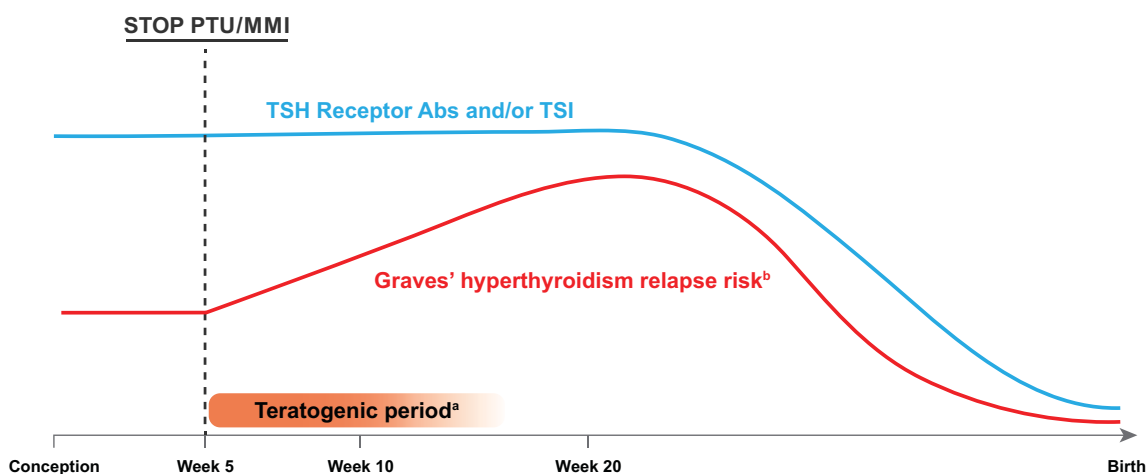
^a When switching from MMI to PTU, a dose ratio of approximately 1:20 should be used (e.g., MMI 5mg once daily = PTU 50mg twice daily).

^b If ATD therapy continues to be required after 16 weeks gestation, it remains unclear whether PTU should be continued or switched to MMI.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

ATD, antithyroid drug; MMI, methimazole; PTU, propylthiouracil; TSH, thyroid stimulating hormone; FT4, free thyroxine; TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin

Women receiving ATD therapy for Graves' disease should confirm pregnancy promptly if suspected and contact their physician, at which time discontinuation of ATD should be considered (Fig. 5). Upon ATD discontinuation, the risk of Graves' hyperthyroidism relapse is 30–70%, depending on the duration of treatment and severity of the



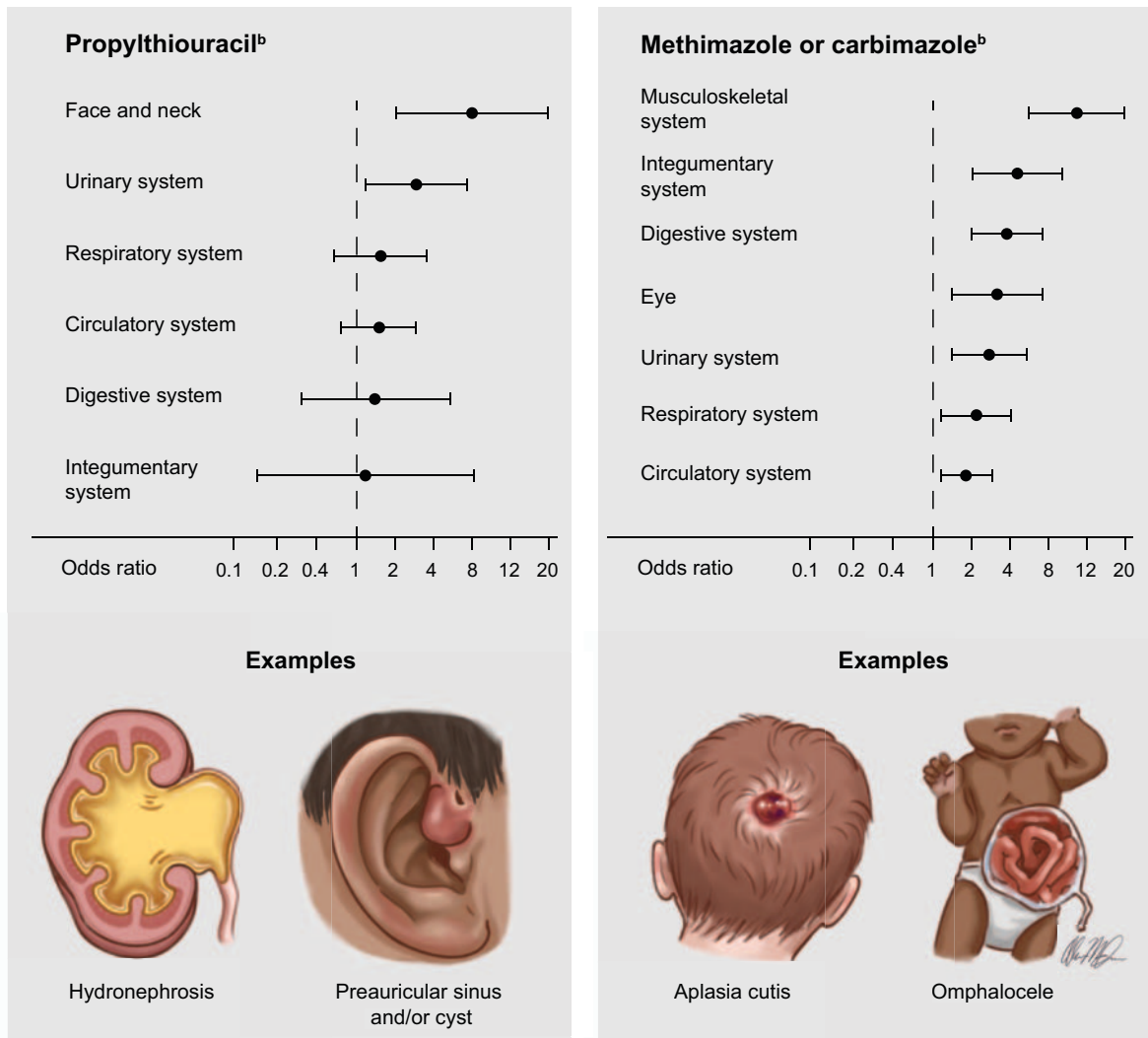
^a For MMI/CMZ, the teratogenic period ends at approximately 16 weeks for skin defects, while the risks for other congenital anomalies remain elevated generally throughout the first trimester.

^b The 1 year risk of Graves' disease relapse typically ranges between 30-70% following ATD discontinuation based on risk factors in the text.

ATD, antithyroid drug; TSHR-Ab, thyrotropin receptor antibody; TSI, thyroid stimulating immunoglobulin

FIG. 5. Strategy for ATD discontinuation upon pregnancy confirmation. Factors important for considering when maternal ATD may be successfully discontinued in pregnancy include the duration and dose of ATD use, maternal TSH concentration, signs of Graves' disease burden (i.e., thyroid eye disease, goiter), and the maternal TRAb and/or TSI concentration. The 1-year risk of Graves' disease relapse typically ranges between 30% and 70% following ATD discontinuation based on these risk factors.

First Trimester ATD Exposure and Congenital Malformation Risks



Prevalence of congenital malformations			
Unexposed ATD group	PTU use only	MMI/CMZ use only	Both PTU and MMI/CMZ
5.9% (N=170,716/2,872,109)	Within 1 year of birth^a		
	7.0% (N=699/9,930)	8.1% (N=91/1,120)	8.0% (N=147/1,841)
5.7% (N=45,982/811,730)	Within 2 years of birth^b		
	8.0% (N=45/564)	9.1% (N=100/1,097)	10.1% (N=16/159)

^a Seo GH, et al. Ann Intern Med 2018;168(6):405-413.

^b Andersen SL, et al. J Clin Endocrinol Metab 2019;104(12):6040-6048.

FIG. 6. Risks of antithyroid drugs during pregnancy. The relative and absolute risks, as well as examples of affected organ systems and severity of congenital malformations, associated with maternal antithyroid drug use during pregnancy are summarized from data reported in two large epidemiological studies. CMZ, carbimazole; MMI, methimazole.

disease at diagnosis. However, as the average time to Graves' hyperthyroidism relapse is about three months, there is a good possibility that the teratogenic window has passed when it is necessary to restart ATDs. Small studies have suggested that low-dose ATD use, stable thyroid function for >6 months before pregnancy²³³ (preferably with serum TSH >0.35), and negative serum TRAb and/or TSI concentration²³⁴ confer the highest chance of remission after ATD withdrawal. After discontinuing ATDs in pregnancy, serum TSH, fT4, and clinical examination may be monitored every one to two weeks in the first trimester, then every two to four weeks in the second and third trimesters. The choice of which ATD may be the safest to continue should be considered, based on data of ATD risks during pregnancy as discussed below.

During pregnancy, if the woman is not a candidate for discontinuation of ATDs, she should receive close monitoring with attempts to decrease the dose or even discontinue ATDs in the second half of pregnancy or, in certain cases, be considered for thyroidectomy. Associated risks of continuing ATD use in pregnancy are important to consider, with congenital malformations being the most relevant (Fig. 6). Three large cohort studies from Denmark and South Korea have shown that both carbimazole (CMZ)/MMI and PTU use in pregnancy are associated with a higher risk of embryopathies, compared with women without Graves' disease.^{214,215,235} In the South Korean cohort, the absolute risks for the prevalence of congenital malformations per 1000 live births increased by 8.8 cases (CI, 3.92–13.70 cases) in the women who took PTU alone, 17.1 cases (CI, 1.94–32.15 cases) for those who took MMI alone, and 16.5 cases (CI, 4.73–28.32 cases) for those who took both PTU and MMI, compared with pregnant women who were not prescribed an ATD.²¹⁵ In addition, the types of abnormalities appear to be milder in those who receive only PTU (i.e., face/neck and urinary tract deformities) compared with those seen with MMI (i.e., deformities spanning seven organ systems; see Fig. 6).²³⁶ Therefore, if PTU is locally available, it is preferred over MMI as ATD therapy in the first trimester.

These studies also showed that the risk of congenital malformations did not differ for pregnancies where MMI was switched to PTU in the first trimester versus those where MMI use was continued throughout the first trimester, suggesting that switching from MMI to PTU may not meaningfully impact the congenital malformation risk.^{214,215,235} In these studies, the switch to PTU in most women happened well into the first trimester (median time, 44 days from pregnancy start in the Danish study²³⁵ but unknown in the Korean study, as the switch between prepregnancy and first trimester was based on prescription data alone²¹⁵) after the

typical time in which the most sensitive aspects of organogenesis have already been completed. It is therefore possible that MMI exposure in early pregnancy was the driving factor underlying these results. In the Korean study, the cumulative MMI dose of >495 mg and longer duration of its use were associated with increased risk of malformations, whereas there were no such associations for PTU.²¹⁵ These data suggest that for those women who continue to require ATD therapy in pregnancy who were not switched to PTU before conceiving, switching from MMI to PTU may lower the risk of congenital abnormalities, especially when switched early in the first trimester or when using a high MMI dose. When switching from MMI to PTU, a dose ratio of approximately 1:20 can be used (e.g., MMI 5 mg/day is equal to PTU 50 mg twice daily). If ATD therapy continues to be required after 16 weeks' gestation (the time of skin closure), it remains unclear whether PTU should be continued or switched to MMI. As both medications are associated with potential adverse effects and switching between the two may potentially result in a period of suboptimal control, we are unable to make a recommendation regarding the choice of a preferred ATD after 16 weeks' gestation.

Women who require continued ATD treatment in pregnancy should be closely monitored with thyroid function testing (serum TSH and fT4 as soon as pregnancy is confirmed and every two to four weeks thereafter) and serum TRAb and/or TSI testing in the first trimester. At each assessment, the decision to continue conservative management of Graves' disease (i.e., holding the ATD and observing) should be guided both by clinical signs/symptoms and thyroid function tests.

Finally, there are limited data on ATD treatment and risks of adverse obstetric outcomes. Both MMI and PTU treatment of Graves' disease lower the risk of miscarriage, preterm delivery, and low birth weight compared with no use of ATDs or uncontrolled hyperthyroidism despite ATD use.²²⁴ The available data regarding ATD risks in women of child-bearing age relate mostly to hepatotoxicity and pancreatitis; although there have been sparse case reports of fulminant hepatic failure associated with PTU use but not MMI in pregnancy, there seem to be no overall differences in hepatotoxicity between women treated with PTU in pregnancy compared with those not exposed to an ATD.²³⁷ There are no data regarding the risks of agranulocytosis and pancreatitis in pregnancy, but they are likely to be similar to those of nonpregnant populations.^{238–240} Baseline liver function tests and a white blood cell count should be obtained whenever an ATD is started, similar to the recommendations for ATD use in nonpregnant individuals.²⁰³

Thyroid surgery for Graves' disease in pregnancy

Recommendations Table 18: Thyroid Surgery for Graves' Disease in Pregnancy	Strength*	Level #
The definitive treatment for Graves' disease during pregnancy with a total thyroidectomy may be considered in exceptional circumstances. ^a	Conditional	Low

^a Including for example in the management of thyroid storm in pregnancy after failing medical management.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

TABLE 5. MONITORING FETAL AND NEONATAL HYPERTHYROIDISM IN PREGNANT WOMEN WITH ACTIVE OR PAST HISTORY OF GRAVES' DISEASE

Group at risk	Recommended monitoring
Pregnant women with active or past Graves' disease (treated with I-131 or total thyroidectomy)	- Measure TRAb and/or TSI in the first trimester, and obtain a monthly fetal ultrasound after 18-20 weeks if the TRAb and/or TSI level remains >3x the upper limit of normal.^a - Continually assess for signs and symptoms of fetal hyperthyroidism by fetal ultrasound.

^a Even in hypothyroid women, high TRAb and/or TSI concentrations can necessitate maternal ATD treatment (as a vehicle to treat or prevent fetal hyperthyroidism) in combination with levothyroxine (to maintain maternal euthyroidism).
TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin

The decision to recommend total thyroidectomy for Graves' disease in pregnancy should be reserved only for exceptional circumstances.²²² Indications include a severe intolerance to ATDs or the inability to control hyperthyroidism with maximum doses of ATDs, which could result in life-threatening hyperthyroidism to the mother and/or hyperthyroidism or hypothyroidism in the fetus (e.g., the latter is more likely if high-dose ATDs are needed to control maternal hyperthyroidism, as in cases of thyroid storm in pregnancy). If thyroid surgery is required imminently, β 1-selective blockers should be used to the extent needed to control maternal hyperadrenergic symptoms of hyperthyroidism, and other therapeutic options (such as potassium iodide,

rare due to pregnancy-specific immune tolerance, especially if serum TRAb and/or TSI titers are less than threefold the upper limit of normal.^{213,216} Although women with a history of Graves' disease that is now in remission (including those who have received a course of ATD) have a low risk of Graves' disease relapse in pregnancy, they should have continued monitoring of thyroid function each trimester and postpartum after three to six months or when developing new thyrotoxicosis symptoms.

Risks of fetal and neonatal hyperthyroidism associated with maternal Graves' disease

Recommendations Table 19: Fetal Hyperthyroidism	Strength*	Level #
Fetal hyperthyroidism may be treated with maternal ATD therapy. In women with underlying hypothyroidism from past I-131 or total thyroidectomy treatment of Graves' disease where maternal ATD therapy is required for the management or prevention of fetal hyperthyroidism, levothyroxine is continued for maintenance of maternal hypothyroidism, while ATD is added for management of fetal hyperthyroidism. Outside of this setting, block and replace therapy is not to be used in pregnancy.	Conditional	Low

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
ATD, antithyroid drug

glucocorticoids, cholestyramine, plasmapheresis) should be considered on a case-by-case approach in a multidisciplinary setting, also taking into account general drug preferences during pregnancy (e.g., using hydrocortisone instead of dexamethasone). Women should be counseled that there are increased risks of surgical complications with thyroid surgery during pregnancy, compared with the nonpregnant state; better surgical outcomes of thyroidectomy during pregnancy are associated with operations performed by high-volume surgeons, compared with low-volume surgeons.²⁴¹

Risk of Graves' disease relapse in pregnancy

Limited data suggest that euthyroid women in pregnancy with a history of remitted Graves' disease have generally similar risks of adverse pregnancy and offspring outcomes to those without a Graves' disease history, with the exception of increased fetal and neonatal hyperthyroidism risks^{213,242} in women who have persistently increased serum TRAb and/or TSI concentrations (which may occur after a total thyroidectomy or previous preconception ¹³¹I treatment).^{224,225}

For women with a history of Graves' disease that is in remission following previous treatment, disease recurrence is

The risks of fetal and neonatal hyperthyroidism are related to maternal TRAbs that cross the placental barrier (Fig. 2) through the neonatal fragment crystallizable receptor (FcRn) and stimulate the fetal thyroid gland. Monitoring for fetal and neonatal hyperthyroidism should be performed if the TRAb and/or TSI concentrations are above three times the upper limit of normal. This also includes, for example, euthyroid pregnant women with a history of past Graves' disease who were definitively treated with a total thyroidectomy or ¹³¹I. In particular, risks of fetal and neonatal hyperthyroidism are higher in cases when the woman received ¹³¹I therapy within two years of conception, as the maternal TRAb concentrations are likely to still be elevated.²⁴³ The indications for monitoring of fetal and neonatal hyperthyroidism in pregnant women with Graves' disease are summarized in Table 5.

Signs of fetal and neonatal hyper- and hypothyroidism are summarized in Tables 6A and 6B. If fetal goiter is found by ultrasound but the diagnosis remains unclear, amniotic fluid or umbilical cord sampling may be considered at 20–24 weeks' gestation. Although umbilical blood sampling better reflects fetal thyroid status than amniotic fluid sampling,^{244–246} it is associated with a 1–2% risk of fetal death,²⁴⁷ and its benefits must be weighed against this risk. Meanwhile, amniotic

TABLE 6. SIGNS AND SYMPTOMS OF FETAL AND NEONATAL HYPERTHYROIDISM (A) AND HYPOTHYROIDISM (B)

A

Fetus	Neonate
- Goiter or thyromegaly (thyroid volume >90-95th percentile), although this finding cannot distinguish between fetal hyperthyroidism and hypothyroidism - Growth restriction - Accelerated bone maturation (distal femoral ossification center visible at <31 weeks) - Craniosynostosis - Heart failure - Fetal hydrops - Cardiomegaly - Tachycardia (persistent heart rate >160-180 beats per minute) [relatively late sign] - Intrauterine demise	- Small for gestational age at birth - Hyperexcitability - Diarrhea - Failure to thrive - Vomiting - Ophthalmopathy - Heart failure and cardiac arrhythmias - Systemic and pulmonary hypertension - Hepatosplenomegaly - Jaundice - Hyperviscosity syndrome - Thrombocytopenia - Craniosynostosis - Small anterior fontanelle

B

Fetus	Neonate ^a
- Goiter, which may be accompanied by hyperextension of the neck and tracheal compression - Polyhydramnios - Delayed bone maturation	- Dull look - Puffy facial features - Thickened tongue - Poor feeding - Constipation - Short stature and/or failure to grow - Poor muscle tone

^a Only a minority of neonates are diagnosed with congenital hypothyroidism based on clinical findings, highlighting the importance of systematic neonatal screening.

fluid sampling is associated with a 0.1% risk of rupture of membranes, and normal fetal thyroid function tests obtained through this route do not completely exclude fetal thyroid dysfunction.²⁴⁸ All cases of fetal and neonatal hyperthyroidism are considered high-risk pregnancies and should be managed by a multidisciplinary team.

For confirmed cases of fetal hyperthyroidism, treatment largely consists of maternal ATDs. In women already receiving LT4 replacement for iatrogenic hypothyroidism from past ¹³¹I treatment or thyroidectomy, maternal ATDs should be given in addition to LT4, as ATDs cross the placenta to impact the fetal thyroid gland (Fig. 2).

Infants born to women with Graves' disease who have maternal serum TRAb concentrations >3× upper limit of normal should be closely followed and monitored for neonatal thyroid dysfunction.^{216,243} If the mother is receiving ATDs, their infants may be initially euthyroid at birth but can become thyrotoxic when the effect of the ATDs dissipates, due to the relatively longer half-life of TRAb and/

or TSI compared with that of ATDs. Risk assessment and follow-up strategies should be made in a multidisciplinary setting involving the endocrinologist, obstetrician, maternal fetal medicine subspecialist, and pediatrician. Neonatal Graves' hyperthyroidism may require ATD treatment and may present with fluctuating hypothyroidism or hyperthyroidism in case of combined stimulating and blocking TRAb. However, treatment is likely to be short-term, as remission of neonatal Graves' disease is common by 20 weeks of life,²⁴⁹ and remission by 48 weeks after birth is nearly always observed.²⁵⁰ Neonates born to a mother with poorly controlled Graves' disease may also develop primary or central hypothyroidism that would require LT4 replacement at birth or upon withdrawal of maternal ATD use.^{251–253}

Postpartum management of Graves' disease

In the postpartum period, there is a swift normalization of the immune system after the period of prolonged immune

tolerance in pregnancy. While serum TRAb and TSI concentrations in women with Graves' disease decline gradually during pregnancy, they are anticipated to increase in the postpartum period, thereby conferring a 25–55% estimated risk of Graves' disease relapse after delivery.²⁵⁴ In addition, some data, though not all, report an increased prevalence of new-onset Graves' disease in the postpartum period.^{255–258} Guidance on the evaluation and management of hyperthyroidism during lactation can be found in Section I.

Autonomous thyroid nodules

treatment-specific effects for ATNs on future fertility outcomes, pregnancy outcomes, or fetal/child outcomes. Overt hyperthyroidism arising from autonomous thyroid nodules in women desiring pregnancy should be treated preconception, either surgically, with focal ablation, or with ¹³¹I. If thyroid surgery is pursued, the woman should be counseled to have at least two consecutive postoperative normal thyroid function tests obtained at least six weeks apart before conceiving. Pregnancy should be avoided for at least six months following ¹³¹I treatment of ATNs, owing to a higher risk of miscarriage and birth defects (as extrapolated from data on ¹³¹I treatment for DTC).²¹⁷ Also after ¹³¹I treatment, stable thyroid function (at least two consecu-

Recommendations Table 20: Autonomous Thyroid Nodules		Strength*	Level #
Preconception			
Overt hyperthyroidism arising from autonomous thyroid nodules in women desiring pregnancy should be treated preconception, either surgically, with focal ablation, or with I-131. ^a	Good Practice Statement		
Pregnancy should be avoided for at least 6 months following I-131 treatment of autonomous thyroid nodules.	Good Practice Statement		
During pregnancy			
Women with overt hyperthyroidism arising from autonomous thyroid nodules during pregnancy should be treated with ATD therapy, targeting a FT4 concentration at or slightly above the upper third of the reference interval. For T3-predominant secreting thyroid nodules, the treatment target is a total or free T3 at or slightly above the upper limit of the reference interval.	Good Practice Statement		

^a The decision regarding surgical or I-131 treatment can depend upon patient preferences including the timing of trying to conceive and risks of complications. Definitive treatment in the preconception phase is important in order to mitigate the risks associated with maternal hyperthyroidism and ATD exposure during pregnancy.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
ATD, antithyroid drug; FT4, free thyroxine; T3, triiodothyronine

Epidemiology and physiology. Overt hyperthyroidism may arise from the presence of an ATN during pregnancy, although this is exceedingly rare. There are no robust data on the risks of adverse pregnancy outcomes in women with ATNs. It is relevant to note that in women with an ATN (either with or without ATD treatment), the maternal thyroid function is not a marker of fetal thyroid status (which is opposite to women with Graves' disease, because in hyperthyroidism due to an ATN, there are no TRAb/TSI that stimulate fetal thyroid hormone production).

Clinical presentation and evaluation. The evaluation and definitive treatment of hyperthyroidism arising from a suspected ATN is difficult during pregnancy and, therefore, should ideally be completed prior to conception. In the rare case when an ATN is suspected during pregnancy, biochemical evaluation and clinical suspicion are the primary diagnostic tools, as thyroid scintigraphy is contraindicated. The typical presentation is the identification of a thyroid nodule by palpation that is associated with persistent suppressed TSH or hyperthyroidism after the first trimester in TRAb and/or TSI negative pregnant women, which may take the form of predominant T3 thyrotoxicosis. In the postpartum setting, guidance about radiopharmaceutical use for the diagnostic evaluation of ATNs during lactation is found in Section I.

Treatment and management. Women with overt hyperthyroidism due to ATNs should be advised to undergo definitive therapy before conception. There are limited data regarding

tive postablative normal thyroid function tests obtained at least six weeks apart) should be confirmed before conceiving. ATDs would not provide definitive correction of the hyperthyroidism arising from ATNs and, similar to guidance for the general population,²⁰³ should not be used as long-term therapy in women desiring pregnancy.

During pregnancy, remission of hyperthyroidism resulting from ATNs is not expected, in contrast to Graves' disease, although the hyperthyroidism may become quiescent due to concurrently increased thyroid hormone needs during gestation. The available evidence regarding treatment options for hyperthyroidism resulting from ATNs during pregnancy is limited, but therapy should largely be medical. During the first trimester, beta-blocker treatment at the lowest effective dose may be used for symptomatic control, and considerations similar to those for GTT can be applied. Should the overt hyperthyroidism from ATNs be persistent, particularly after the first trimester, ATD treatment may be considered, weighing the risks of untreated or undertreated maternal hyperthyroidism against the risks of fetal and neonatal thyroid dysfunction. If employed, ATD therapy should be given to target serum fT4 concentrations to the upper third of the reference interval or slightly above,²⁰⁷ along with monthly fetal ultrasound monitoring. The fetus is at higher risk of developing hypothyroidism with maternal ATD therapy given for an ATN, compared with Graves' disease, due to the absence of TRAb and/or TSI in this scenario, which would have counteracted the effect of ATD on the fetal thyroid.

Thyroid surgery for the treatment of ATNs should be reserved in pregnancy only for exceptional circumstances,²²² similar to the surgical indications of Graves' disease in

pregnancy. It is important to note that previous hemithyroidectomy or RAI treatment is an indication for TSH testing upon a positive pregnancy test (Table 1). Finally, there is emerging evidence regarding the safety and efficacy of using minimally invasive techniques such as RFA and ethanol ablation in the treatment of ATNs in pregnant patients. One case series described the restoration of euthyroidism following percutaneous ethanol injection therapy in 2 pregnant women with ATNs,²⁵⁹ which could be considered in refractory cases or if the risks of using ATDs outweigh the benefits. There are limited studies reporting the use of thermal ablative techniques (during pregnancy preferentially with a bipolar probe or monopolar probe and grounding pad) in this setting, and their comparative efficacy and safety during pregnancy versus thyroid surgery are unknown. Treatment of ATNs using ¹³¹I is contraindicated in pregnancy. Guidance about radiopharmaceutical treatment of ATNs during lactation is found in Section I.

H. Thyroid Nodules and Cancer Preconception, In Pregnancy, and Postpartum

Thyroid nodules and thyroid cancer found during preconception, pregnancy, and lactation present unique challenges to both the clinician and the mother. Weighing the pros and cons of pursuing a more immediate plan to make a definitive diagnosis and potentially implement treatment, versus delaying these decisions to either after pregnancy and/or the peripartum period, is pivotal. Shared decision-making is needed to determine which diagnostic tests and treatment interventions should be performed more urgently and to what extent they may adversely impact the mother, fetus, and/or maintenance of pregnancy if carried out. Due to the general absence of high-quality evidence regarding the evaluation and management of women with thyroid nodules and thyroid cancer during preconception, pregnancy, and lactation, this committee has generally combined the available low-quality data in pregnant women with practice recommendations that are in place for nonpregnant individuals to provide guidance on this topic.

What is new in this guideline: (1) Greater emphasis is placed on applying the same considerations in the management of thyroid cancer during pregnancy as one would make outside of pregnancy, particularly given that the vast majority of thyroid cancers are low-risk. (2) In the rare case of a pregnant patient who requires urgent thyroid surgery, this operation should be performed at the time required. While new anesthesia recommendations published since the past iteration of these guidelines endorse that surgery requiring general anesthesia can be performed safely during any trimester, it is still best to proceed with such surgery in the second trimester if possible. First-trimester miscarriage may be incorrectly attributed to surgery (as miscarriage rates are high in the first trimester), and fetal monitoring is warranted during surgery in the third trimester when the fetus is postviability and there may be a risk of needing an urgent delivery. (3) Recent guidelines from the United States and United Kingdom advise that lactating women who undergo surgery can begin breastfeeding as soon as they are awake enough to hold the baby, which is different from prior recommendations that advise the disposal of breastmilk for 24 hours after receiving anesthesia.

Epidemiology and physiology

Observational studies drawn from both iodine-deficient and -sufficient regions report a similar prevalence of thyroid nodules

between pregnant and nonpregnant women,^{260,261} with estimates ranging from 9% to 33% upon screening, but of which only a minority (~6%) are clinically significant.²⁶² Greater age,²⁶³ and associated with this, higher parity,²⁶⁴ are the most relevant risk factors for the detection of a thyroid nodule during pregnancy. For thyroid nodules detected during pregnancy, their size, total number, and frequency of suspicious sonographic features are similar to those of nonpregnant women.²⁶¹ Limited data suggest that the prevalence of nonautonomous thyroid nodules increases with each trimester of pregnancy.²⁶³ There are no rigorous data regarding the prevalence of ATNs in pregnant women, but it is understood that they are generally more likely to be present in those living in iodine-deficient regions.²⁶⁵ ATNs (including multinodular goiter) have an estimated yearly incidence of 1–18 per 100,000 among nonpregnant women aged 20–39 years.^{200,201}

In women with a known history of or new diagnosis of thyroid cancer prior to pregnancy, most of the literature supports that pregnancy itself does not adversely affect overall thyroid cancer outcomes. The size of a thyroid tumor may increase slightly during pregnancy, but the increase is usually not clinically significant.^{266,267} Diagnosis during pregnancy does not appear to be associated with the presenting stage of thyroid cancer,²⁶⁸ and for most patients diagnosed with DTC during pregnancy, delaying treatment until postpartum does not appear to impact achieving an excellent response to therapy.²⁶⁹ Furthermore, the physiology of pregnancy does not appear to be associated with thyroid cancer progression or recurrence in pregnant women with DTC who have previously received initial treatment (i.e., surgery with or without RAI therapy). The risks of recurrence, clinically significant progression of DTC, and progression-free and overall survival are generally similar between nonpregnant patients and pregnant patients who have a history of or are diagnosed with DTC during pregnancy.^{270–273} Progression of DTC during pregnancy is predicted by the presence of a structurally or biochemically incomplete response to therapy at the time of conception,²⁷⁴ similar to the considerations of DTC risk used for the nonpregnant patient. Women at high risk for disease progression or immediate complications during pregnancy include those with distant metastatic disease and/or grossly invasive DTC on neck ultrasound or other imaging.

Clinical presentation and evaluation

Thyroid ultrasonography remains the most accurate and sensitive tool for the detection or confirmation of a palpated thyroid nodule in women during preconception or pregnancy. Upon discovery of a thyroid nodule, serum TSH should be measured to rule out possible hyperthyroidism arising from an autonomously functioning thyroid nodule. The definitive diagnosis of an autonomously functioning thyroid nodule cannot be made during pregnancy, given the contraindication to any radioisotope use, including scintigraphy and the common occurrence of physiological (subclinical) hyperthyroidism (Section C).

For nonfunctioning thyroid nodules detected during preconception and pregnancy, evaluation for malignant risk is generally similar to that of nonpregnant individuals. Obtaining a history of risk factors for thyroid cancer, as well as assessment for any relevant syndromic or familial risks, should be performed. There is a possible positive association

between higher parity and the risk of thyroid cancer, but this is likely not clinically significant, and studies are complicated by residual confounding factors (age, breastfeeding, thyroiditis, obesity, other factors).^{275,276} If indicated by sonographic risk criteria, fine-needle aspiration (FNA) biopsy to evaluate the malignant potential of a thyroid nodule should be completed prior to pregnancy. The patient may be counseled to maintain contraception until the planned evaluation and/or treatment are complete, although the clinical suspicion for advanced disease and possible decreased reproductive potential of the patient should be weighed in this consideration. If the patient is pregnant when a nodule is identified, FNA biopsy may be performed after shared decision-making, taking into account subsequent management options of its results.

The anticipated slight enlargement of the thyroid gland during pregnancy (especially during the first trimester)^{261,263,277} should be considered when evaluating the malignant risk of a thyroid nodule. For nontoxic thyroid nodules, the sonographic risk of malignancy (estimated by tools such as the ATA thyroid nodule risk stratification system²⁷⁸ and American College of Radiology Thyroid Imaging Reporting and Data System criteria²⁷⁹) is not different between pregnant and nonpregnant individuals. However, since overall survival appears not to differ if surgery is performed during or after delivery in pregnant women with thyroid cancer, patient preference for the timing of FNA biopsy (i.e., during pregnancy or postpartum), as well as sonographic features, should be taken into account. For pregnant women who undergo

FNA biopsy and are found to have a cytologically indeterminate thyroid nodule, pregnancy is neither associated with a higher rate of malignancy nor the initial stage of thyroid cancer.^{268,271,280} As molecular marker tests of cytologically indeterminate thyroid nodules have not been validated for use in pregnancy, their diagnostic performance is unknown in this setting.

Management of benign thyroid nodules

Recommendations for the management of ATNs during preconception and pregnancy are discussed in Section F. Appropriate evaluation and treatment (thyroid surgery and/or thermal ablation therapies) of benign, nonfunctional thyroid nodules should ideally be completed prior to pregnancy (*refer to the ATA 2026 thyroid nodule guidelines*). While thyroid surgery does not change the outcome of a future pregnancy, untreated or incompletely treated postoperative hypothyroidism and hypocalcemia secondary to permanent maternal hypoparathyroidism would increase the obstetrical and offspring risks of pregnancy (see Section F). For pregnant women with nonfunctional thyroid nodules that become symptomatic during pregnancy (e.g., associated compressive symptoms to the anterior neck or rapid nodule growth), shared decision-making should weigh the risks and benefits of these therapies during pregnancy.

Management of DTC preconception and in pregnancy

Recommendations Table 21: Differentiated Thyroid Cancer		Strength*	Level #
<i>Preconception</i>			
Patient-tailored preconception counseling about the effects of DTC treatment options on fertility and future pregnancy should be provided, including the potential risks of preconception I-131 administration on ovarian function.		Good Practice Statement	
In women who desire a future pregnancy, any required initial treatments of DTC should be completed preconception, while maintaining contraception.		Good Practice Statement	
The decision to administer postoperative I-131 treatment of DTC during preconception or to postpone until after pregnancy should be guided by DTC risk. ^a		Good Practice Statement	
Pregnancy should be avoided for at least 6 months following RAI treatment of DTC. In women who conceive within 6 months of receiving I-131, fetal monitoring for malformations should be considered.		Good Practice Statement	
The same DTC risk-based TSH suppression goals should be used for women planning pregnancy as for the general population, though not exceeding 2.5 mU/L.		Good Practice Statement	
<i>Pregnancy</i>			
Pregnant women with biopsy-suspicious thyroid nodules or biopsy-proven DTC, who do not have a high risk of thyroid cancer progression or impending tumor-related complications based on the anatomic location of the tumor, may be counseled to delay thyroid surgery until the postpartum period.		Conditional	Very Low
For DTC in pregnancy with a high risk of progression or immediate complications, the decision to undergo surgery may be based on oncologic indications, similar to if the patient was not pregnant.		Conditional	Very Low
Pregnant women with DTC may have the same TSH goal as was determined preconception, with TSH monitoring approximately every 4 weeks during the first half of pregnancy, at least once in the third trimester, and every 4-6 weeks after any dose adjustment.		Conditional	Low
Pregnant women with DTC may be followed using the same measures and frequency of cancer surveillance as was followed during preconception, with the exception of radioisotope imaging that is contraindicated.		Conditional	Very Low

^a For intermediate-risk DTCs, it may be reasonable to delay postoperative I-131 treatment if imminent pregnancy is desired in a woman near the end of her reproductive span or with suboptimal fertility, which should be discussed in shared decision-making with the patient. For high-risk DTCs, the decision to administer I-131 therapy in the short-term or delay until after pregnancy is complete is best determined in multidisciplinary discussion. I-131 treatment cannot be administered during pregnancy or lactation.

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
DTC, differentiated thyroid cancer; RAI, radioactive iodine; TSH, thyroid stimulating hormone

TABLE 7. GUIDANCE FOR THE MANAGEMENT OF DTC PRECONCEPTION

Therapy	Guidance
Thyroid surgery	Thyroid surgery for suspicious thyroid nodules and/or thyroid cancer should ideally be completed by a high-volume surgeon before conception. A patient-centered, multidisciplinary discussion can help determine optimal DTC management in the context of pregnancy planning.
Postoperative RAI treatment	Women should be advised to wait at least 6 months after I-131 treatment of DTC before conceiving, to avoid the potential adverse effects of radiopharmaceutical use on future pregnancy.
TSH suppression	Preconception serum TSH should be targeted to that recommended for the risk stratification of DTC though not exceeding 2.5 mU/L, as would be advised to patients not considering pregnancy.
DTC monitoring	- Women with a non-operated DTC should be counseled that the tumor size may increase slightly (though usually not in a clinically significant manner) during gestation. Patients with persistent or metastatic DTC desiring pregnancy should be managed in the context of a patient-centered, multidisciplinary approach and a desired pregnancy planned once disease is relatively stable. - Women who have received a total thyroidectomy for the treatment of DTC should be counseled that serum thyroglobulin concentrations may increase slightly during pregnancy;²⁸⁵ but are likely to return to their previous concentrations after delivery.
Treatment of advanced DTC	Data regarding fertility risks of targeted systemic therapies are extremely limited.

DTC, differentiated thyroid cancer; RAI, radioactive iodine; TSH, thyroid stimulating hormone

Women of childbearing age with a new diagnosis of DTC who desire pregnancy should be counseled on the potential effects of thyroid cancer treatment (e.g., the extent and risks of thyroid surgery, possible postoperative ¹³¹I treatment, and extent of TSH suppression) on fertility and future pregnancy (Tables 7 and 8). Data regarding the efficacy and safety of ablative and targeted systemic therapies in this population are extremely limited.

In women undergoing IVF/ICSI, limited data suggest that prior treatment of papillary thyroid cancer (PTC) is associated with a reduction in the number of retrieved oocytes per cycle and a lower number of high-grade

embryos compared with women who have not received treatment for PTC, in analyses adjusted for age, BMI, concomitant fertility factors, and ART protocols.²⁸¹ One small study has reported that women undergoing IVF/ICSI were more likely to have a clinical pregnancy or live birth following hemithyroidectomy, compared with those who had a total thyroidectomy.²⁸² Otherwise, there appear to be no independent risks from postoperative RAI treatment or TSH suppression on ART outcomes. No data are available regarding the potential risks of advanced DTC therapies (i.e., targeted systemic therapies) in women undergoing ART.

TABLE 8. GUIDANCE FOR THE MANAGEMENT OF DTC IN PREGNANCY

Therapy	Guidance
Thyroid surgery	- For most patients with DTC diagnosed during pregnancy, delaying treatment until postpartum does not impact thyroid cancer outcomes. - If thyroid surgery is recommended in pregnancy, a patient-centered plan that incorporates case timing and fetal safety should be discussed in a multidisciplinary setting.
Postoperative RAI treatment	Radiopharmaceutical use in pregnancy is absolutely contraindicated.
TSH suppression	- Postoperative TSH suppression requires a balance of maternal DTC treatment goals and risk of excessive levothyroxine exposure to the fetus. - Levothyroxine overtreatment in pregnancy increases the risk of pregnancy-induced hypertension, preeclampsia, preterm delivery, and fetal complications (e.g. low birth weight and adverse neurodevelopmental measures).^{34,35,171,173} - There is limited evidence regarding the optimal strategies for maintaining LT4 suppression therapy during pregnancy in women with DTC.
DTC monitoring	DTC monitoring in pregnant women should generally follow the same measures as in non-pregnant patients.
Ablative techniques	There are insufficient data to determine if RFA and other thermal ablation techniques for thyroid cancer therapy may affect pregnancy outcomes.
Treatment of advanced DTC	Most targeted therapies are contraindicated for use in pregnancy. Risks and benefits of treatment of advanced DTC during pregnancy should be discussed in a multidisciplinary environment weighing the risks of disease treatment with the safety of the mother and fetus.

DTC, differentiated thyroid cancer; RAI, radioactive iodine; TSH, thyroid stimulating hormone; LT4, levothyroxine; RFA, radiofrequency ablation

Thyroid surgery. Surgery for thyroid nodules and/or thyroid cancer during preconception is generally considered safe and is not associated with the health of a future pregnancy.²⁸⁴ In women with biopsy-proven DTC who have not yet undergone treatment and who become pregnant, there is typically little urgency to perform immediate thyroid surgery before delivery. The vast majority of low-risk DTC (microPTCs) monitored by active surveillance remains stable in size or even becomes smaller during the gestational period, with only 8% growing ≥ 3 mm during gestation.²⁶⁷ Therefore, for most women diagnosed with DTC during pregnancy, it is generally reasonable to delay thyroid surgery until the postpartum period for the benefit of both the mother and fetus. If there is a high risk of thyroid cancer progression or impending complications from the tumor, urgent thyroid surgery can be safely performed regardless of trimester,²⁸⁵ although the second trimester remains preferred, with the surgical plan ideally discussed in a multidisciplinary setting to optimize case timing and fetal safety. Preoperatively, for pregnant women already receiving LT4, the dose may be increased by 25–50 mcg/day, depending on their body weight and preoperative TSH level. For pregnant women who are not already taking LT4 and planned to undergo a hemithyroidectomy, starting LT4 50 mcg once daily either immediately postoperatively or upon the results of a TSH measurement 4 weeks after surgery may be considered. For pregnant women who are not already taking LT4 and planned to undergo a total thyroidectomy, LT4 should be started immediately after thyroid surgery at 1.5–1.7 mcg/kg/day, plus an additional 20–30% dose increase as required for gestation.

Permanent hypoparathyroidism may occur in up to 7% of patients undergoing total thyroidectomy, with a higher risk in patients with thyroid cancer, those undergoing neck dissection, and those undergoing thyroidectomy with a low-volume surgeon.²⁸⁶ Hypoparathyroidism can be a risk for obstetric complications, such as preterm birth and congenital anomalies compared with women without hypoparathyroidism.²⁸⁷ Maternal hypocalcemia due to hypoparathyroidism can result in fetal secondary hyperparathyroidism with bone demineralization, uterine contractions, and increased risk of miscarriage.²⁸⁸ These potential maternal and fetal complications should be considered when planning the extent of thyroid surgery in patients desiring pregnancy.

Postoperative ¹³¹I treatment. The considerations regarding the optimal timing of postoperative ¹³¹I treatment in women who wish to conceive relate primarily to fertility and pregnancy outcomes. Studies of individuals with DTC have inconsistently shown that a slight delay of ¹³¹I administration (defined as >3 months postsurgery) may increase the risk of an incomplete response to DTC treatment,^{289,290} although there do not appear to be any differences in overall survival.^{291–293} Limited studies report inconsistent associations between the administration of ¹³¹I and ovarian reserve (as defined by serum anti-Müllerian hormone [AMH] concentrations). A meta-analysis²¹¹ showed lower AMH concentrations^{212,294–296} and slightly earlier menopause after RAI administration in some studies, including in women aged >35 years compared with those aged <35 years and in women who have received multiple ¹³¹I treatments, while

other data report that postoperative RAI remnant ablation and TSH suppression do not appear to impact the efficacy of ART or result in lower serum AMH concentrations ascertained at 3–12 months after ¹³¹I treatment for DTC.²⁸² Reassuringly, permanent ovarian failure is extremely unlikely after ¹³¹I treatment.²⁹⁷

Observational studies have reported lower pregnancy rates among women who received ¹³¹I ablation for DTC, compared with those who have not received ¹³¹I,^{298,299} while other data show that there are no differences in pregnancy rates nor increased risks of miscarriage, preterm birth, stillbirth, or congenital malformations related to the use of ¹³¹I.^{211,300,301} Data suggesting the association between pregnancy loss and ¹³¹I administration may be related to the timing of ¹³¹I treatment. Some studies have shown increased rates of pregnancy loss occurring within the first 12 months after ¹³¹I administration (although many did not distinguish between spontaneous or therapeutic abortion),³⁰⁰ while a large population-level South Korean study showed that pregnancy loss is observed only if conception occurs <6 months after ¹³¹I administration.²¹⁷ Although there does not appear to be an increase in congenital anomalies among women who conceive within six months of ¹³¹I therapy for thyroid cancer,³⁰¹ the higher rates of abortion may conceal the true risk of congenital anomalies, and these data must be interpreted in the context of a patient's baseline obstetric risk. Finally, there is a lack of conclusive evidence regarding the impact of ¹³¹I treatment on later offspring development and growth, regardless of whether women undergo ART or conceive naturally following the ¹³¹I dose. Taken together, current evidence suggests that waiting at least six months after ¹³¹I treatment before attempting pregnancy would alleviate most pregnancy-related risks associated with ¹³¹I administration. The potential impacts of ¹³¹I administration on fertility and on later offspring adverse effects are less clear.

TSH suppression. Pregnancy planning is best done when the serum TSH concentration is at the target goal of DTC management that was established preconception,^{302,303} while taking into account the considerations surrounding thyroid surgery as summarized above in the “Thyroid Surgery” subsection. Women with DTC who have already undergone thyroid surgery and become pregnant should continue LT4, but balancing the potential maternal oncologic risks of inadequate TSH suppression and excess T4 exposure to the fetus requires thoughtful clinical care and monitoring. It has been understood that mildly decreased TSH concentrations during pregnancy may be similar to the physiological effects of hCG and that subclinical hyperthyroidism rarely poses a risk to pregnancy.²¹⁸ However, there are newer data that suggest possible risks if preconception TSH concentrations (i.e., measured 6–12 months before pregnancy) are abnormal. In two large population-level observational studies, abnormal TSH concentrations (defined in this cohort as <0.10 or >2.49 mU/L) in women during preconception were associated with delayed time to achieve pregnancy and increased risks of spontaneous abortion, preterm birth, small for gestational age, birth defect, and perinatal infant death.^{103,104} Preconception TSH concentrations <0.1 mU/L, but not those above, were associated with a longer time to pregnancy over a one-year period.¹⁰⁴ In general, it is

reasonable to target the same TSH goal in pregnancy as was determined preconception, according to risk stratification of the DTC, and monitor TSH with the same frequency as in the pregnant woman without DTC (see Section F).

Monitoring of DTC during pregnancy. Given the evidence presented above demonstrating that the physiology of

ablation, for the treatment of thyroid cancers in pregnancy are extremely sparse.

Management of thyroid cancer in lactation

Although there are fewer direct risks of maternal DTC treatment options to the breastfed infant compared with the

Recommendations Table 22: Thyroid Cancer in Lactation		Strength*	Level #
If thyroid cancer surgery is indicated during lactation, a patient-centered anesthesia plan as well as the risks and benefits of continued breastfeeding versus delaying surgery until lactation is completed should be discussed in a multidisciplinary fashion.		Good Practice Statement	
If postoperative I-131 ablation is indicated during lactation, a patient-centered plan considering the risks and benefits of delaying I-131 treatment in order to continue breastfeeding should be discussed in a multidisciplinary fashion.		Good Practice Statement	
The same DTC risk-based TSH suppression goals should be used for breastfeeding women as for the general population.		Good Practice Statement	
Lactating women who are recommended to receive targeted systemic DTC therapies should be counseled about the need to discontinue breastfeeding. ^a		Good Practice Statement	

^a If breastfeeding should be stopped, consider dopamine agonist therapy to reduce symptomatology related to abrupt breastfeeding cessation

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

DTC, differentiated thyroid cancer; TSH, thyroid stimulating hormone

pregnancy does not appear to be associated with clinically significant progression of DTC or progression-free or overall survival.^{270–273} DTC monitoring in pregnant women should generally follow the same measures as nonpregnant patients. Women with structural or biochemical DTC or metastatic disease have similar risks of progression during pregnancy as nonpregnant women.^{270,304} Furthermore, disease progression during pregnancy can be predicted by disease behavior prior to pregnancy.³⁰⁵ These considerations should be discussed with a multidisciplinary treatment team to permit reasonable monitoring during pregnancy in such patients. Women with grossly invasive DTC on neck imaging preconception are at the highest risk for disease progression or immediate complications during pregnancy, similar to these risks in nonpregnant individuals.

Treatment of advanced DTC with targeted systemic therapies. There are insufficient data to determine if therapies for advanced thyroid cancer may affect fertility or pregnancy outcomes. Data on the use of thermal ablative techniques, including RFA, ethanol ablation, and laser

fetus during pregnancy, several considerations are pertinent to consider. Thyroid surgery performed during lactation is considered generally safe, as only clinically insignificant amounts of anesthetic drugs are transferred into breastmilk and are not thought to pose a danger to the breastfeeding infant. Current guidelines from the United States and United Kingdom advise that lactating women who undergo surgery can begin breastfeeding as soon as they are awake enough to hold the baby,²⁸⁵ which is different from prior recommendations advising the disposal of breastmilk for 24 hours after receiving anesthesia. Considerations regarding postoperative ¹³¹I ablation and the treatment of maternal postoperative (± postablative) hypothyroidism in breastfeeding women are discussed in Section I.

Finally, there are no data on the use and safety of RFA for the treatment of thyroid cancer during lactation. The concentrations of targeted systemic therapies in human breastmilk, or if there may be adverse effects of maternal targeted therapy use on breastmilk production or the health outcomes of the breastfed child, also remain unknown. Serious adverse reactions of maternal use of these therapies to the breastfed infant remain an undetermined possibility.

Medullary and advanced thyroid cancers

Recommendations Table 23: Medullary and Advanced Thyroid Cancers		Strength*	Level #
<i>Medullary thyroid cancer and pregnancy</i>			
Women diagnosed with MTC should undergo initial management (including thyroid surgery) prior to pregnancy and maintain contraception until this is complete.		Good Practice Statement	
Women diagnosed with MTC should undergo genetic testing prior to pregnancy.		Good Practice Statement	
Routine surveillance of postoperative MTC in pregnancy is similar to the non-pregnant patient. However, due to a possible pregnancy and lactation-related increase of serum calcitonin concentrations, monitoring may also include serum CEA concentrations during pregnancy and postpartum until breastfeeding is complete.		Conditional	Very Low
<i>Advanced thyroid cancers in pregnancy</i>			
The same urgency should be applied to pursuing thyroid surgery, EBRT, and/or systemic therapy for poorly differentiated and anaplastic thyroid cancers in pregnant women as in non-pregnant individuals, with case-by-case considerations in a multidisciplinary discussion weighing the expected risks of delaying treatment versus the fetal/maternal risks.		Good Practice Statement	

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

MTC, medullary thyroid cancer; CEA, carcinoembryonic antigen; EBRT, external beam radiation therapy

The relatively rare scenario of a newly diagnosed medullary or advanced thyroid cancer in a pregnant woman requires careful consideration, balancing the risks and benefits of treatment options during this critical life stage. All decisions should be made in the context of a multidisciplinary team, including a maternal fetal medicine subspecialist if available, on a case-by-case basis, weighing the risks and benefits to the mother and the fetus.

Clinical presentation and evaluation. Serum calcitonin testing in the setting of a thyroid nodule should only be performed if there is a specific indication to do so (i.e., family history of either medullary thyroid carcinoma, MEN2, or a known *RET* gene mutation). Of note, relevant positive history and physical examination findings in a pregnant woman with thyroid nodules could be related to genetic abnormalities (i.e., MEN2, Cowden's disease, familial adenomatous polyposis, Carney complex) and may be an indication for newborn screening. The presentation of a poorly differentiated or anaplastic thyroid cancer in a woman during preconception or pregnancy is expected to be similar to that of the general patient with advanced thyroid cancers.

Treatment and management. Patients with MTC should be advised to undergo usual treatment, including thyroid surgery and any recommended genetic testing, prior to pregnancy. The risk of MTC progression in pregnant patients who have received their initial treatment preconception is similar to that of nonpregnant women; thus, the same surveillance strategies can be applied in pregnancy. However, it is important to note that serum calcitonin concentrations may be altered during pregnancy. Studies of serum calcitonin concentrations followed longitudinally in pregnant patients without MTC are inconsistent; while some report that calcitonin remains similar to the nonpregnant patient,³⁰⁶ others report significant calcitonin elevation during the second trimester of pregnancy that continues through lactation. Serum calcitonin concentrations can increase as much as two to three times the upper limit of normal during pregnancy and remain elevated during the postpartum period, especially if breastfeeding.^{86,307,308} In

contrast, serum carcinoembryonic antigen concentrations appear to remain stable during pregnancy and may be a more reliable tumor marker until lactation is complete. The pentagastrin stimulation test for patients with suspected MTC and normal serum calcitonin concentrations is contraindicated in pregnancy.³⁰⁹

Data on patients with unresectable or poorly differentiated/anaplastic thyroid cancer or metastatic MTC desiring conception or during pregnancy are scarce. It is generally advisable, when possible, to apply the same urgency to the treatment of poorly differentiated/anaplastic thyroid cancer in pregnant women as in nonpregnant women. External beam radiation therapy can be considered in the setting of a locally advanced thyroid cancer, with a preference to use this treatment during the first trimester to minimize fetal exposure. Based on animal studies, tyrosine/multikinase inhibitors have the potential to cause fetal harm when administered in pregnancy. The pregnancy risks of checkpoint inhibitors used to treat some thyroid cancers are classified as either the inability to rule out harm (as seen with ipilimumab) or even fetal death (as seen with anti-PD1 inhibitors) in animal studies, with extremely limited human data reporting an increased risk of prematurity and low birth weight with their use.³¹⁰ The World Health Organization pharmacovigilance database of 91 pregnancies exposed to immune checkpoint inhibitors in pregnancy to June 2022 reported no increased incidence of adverse pregnancy, fetal, and/or newborn outcomes, compared with other anticancer treatments.³¹¹ As the available human data regarding the potential effects of these drugs are sparse, pregnant women should be advised on the risks of embryotoxicity, fetotoxicity, and teratogenicity. These agents should generally not be advised in most pregnant patients, but in those with advanced disease, their potential benefits in stabilizing tumor burden may outweigh their exposure risks.

I. Thyroid Dysfunction Postpartum

What is new in this guideline: (1) In these guidelines, we place greater emphasis on shared decision-making and the role of the patient to be better informed on the signs, symptoms, and natural time course of PPT. (2) We have

also provided greater detail regarding differences in the recommended durations of breastfeeding cessation related to radiopharmaceutical use in lactating women, should it be required for diagnostic or treatment purposes in Graves' disease or DTCs.

Postpartum thyroiditis

between four and eight months postpartum, in which typical symptoms of hypothyroidism may occur in some individuals, and is followed by the last phase when there is gradual restoration of euthyroidism over another two to three months.

Epidemiology and physiology. The estimated prevalence of PPT is 8%, although this estimate is based primarily on

Recommendations Table 24: Postpartum Thyroiditis	Strength*	Level #
TPOAb-positive women or those with a history of PPT may be educated about the high risk of PPT (recurrence) and symptoms that may warrant thyroid function testing.	Conditional	Low
During the thyrotoxic phase of PPT, women with hyperthyroidism-related symptoms should be treated with the lowest effective dose of a beta-blocker (propranolol or metoprolol may be used if lactating).	Strong	High
Levothyroxine may be considered during the hypothyroid phase of PPT if the woman is symptomatic, breastfeeding, or if pregnancy is planned within 6 months.	Conditional	Low
Upon normalization of thyroid function tests after PPT, thyroid function testing should be repeated after one year or upon the development of any hypothyroidism-related symptoms.	Good Practice Statement	

* Strength of Recommendation; # Level of Evidence; Good Practice Statement
TPOAb, thyroperoxidase antibody; PPT, postpartum thyroiditis

PPT is defined as a characteristic pattern of (transient) autoimmune thyroid dysfunction occurring within 12 months after delivery, although it may also occur after a pregnancy loss (Fig. 7). The classic triphasic pattern of PPT, similar to other forms of thyroiditis, comprises an initial period of destructive thyrotoxicosis arising from painless release of preformed thyroid hormone from the inflamed thyroid gland, usually appearing between one and six months postpartum. This is followed by a hypothyroid phase that usually occurs

observational studies that have focused on clinically apparent disease,³¹² much of PPT is likely to be unidentified. Risk factors for developing PPT include a history of PPT, known thyroid autoimmunity (as defined by serum TPOAb positivity³¹³ or heterogeneous echotexture by thyroid ultrasound), personal history of autoimmune disease, and a family history of autoimmune thyroid disease. The most prominent risk factor is TPOAb positivity (in studies assessed in the first trimester), increasing the risk of PPT to

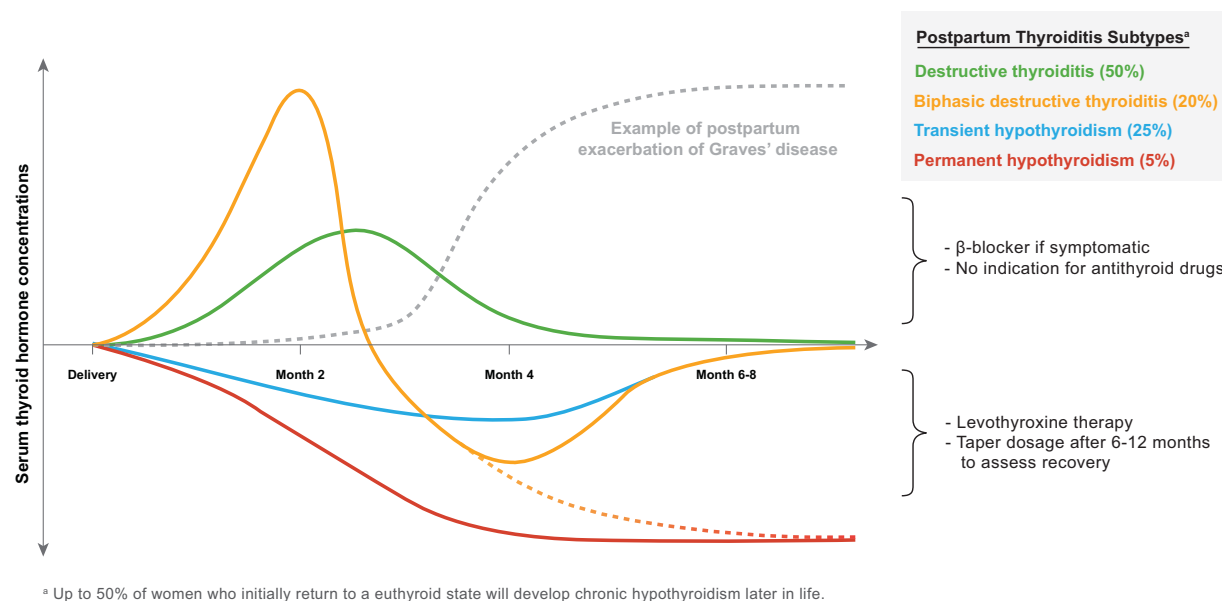


FIG. 7. Trajectories of postpartum thyroiditis subtypes. The typical trends of serum thyroid hormone concentrations seen in various subtypes of postpartum thyroiditis are summarized. During the thyrotoxic phases of the destructive subtypes, antithyroid drugs are not indicated, as the underlying etiology is not increased thyroid hormone production (as compared with the postpartum recurrence or exacerbation of Graves' disease, shown in the gray dotted line). During the hypothyroid phase of thyroiditis, a short course of thyroid hormone replacement may be considered in women with profound symptoms of hypothyroidism, with the plan to taper or stop the dose after 6–12 months.

TABLE 9. DISTINGUISHING BETWEEN THE THYROTOXIC PHASE OF POSTPARTUM THYROIDITIS (PPT) AND GRAVES' DISEASE

Feature	Thyrototoxic (destructive) phase of PPT	Graves' disease
Onset of thyrotoxicosis	1-6 months after delivery	3-12 months after delivery
TRAb and/or TSI concentration	Negative	Positive in most
Hyperthyroid symptoms	Usually mild	Can be severe
Eye symptoms	Absent	Can be present
Hyperthyroid signs	May be absent	May be present, along with specific signs of Graves' disease ^a
Duration of thyrotoxic phase	0-3 months	>3 months
TT3 (ng/dL) to TT4 (mcg/dL) ratio ³²⁹	Typically <20	Typically >20
Thyroid vascularity by ultrasound	Low	High
Radioactive iodine uptake ^b	Low or absent	High

^a Diffuse goiter, thyroid bruit, pretibial myxedema, and/or thyroid eye disease

^b Contraindicated if the woman is lactating, thus temporary discontinuation of breastfeeding would be needed following administration of the radioisotope

PPT, postpartum thyroiditis; TRAb, TSH receptor antibodies; TSI, thyroid stimulating immunoglobulin; TT3, total triiodothyronine; TT4, total thyroxine

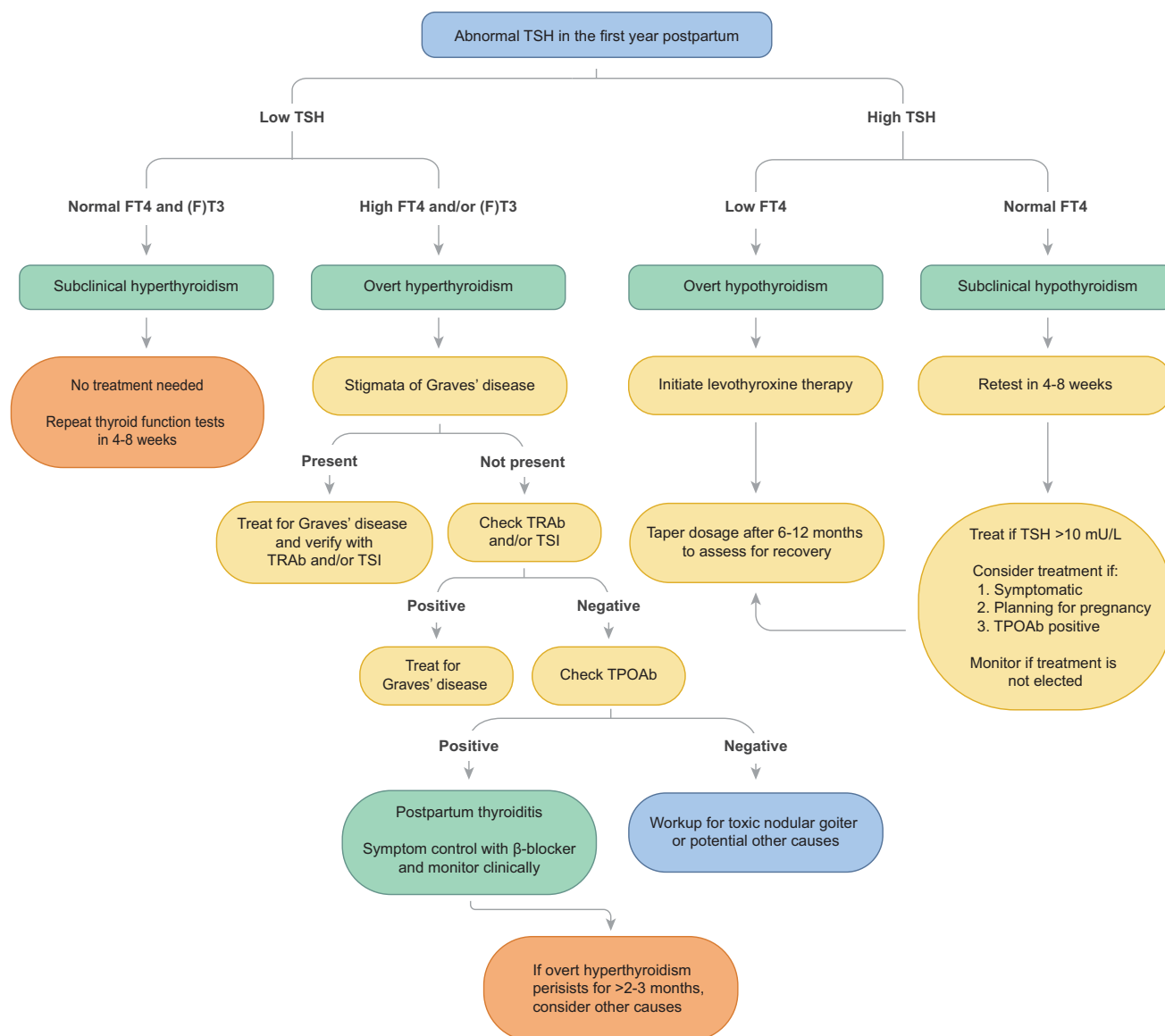
33–50%.³¹⁴ The autoimmune basis of PPT reflects the rebound of the immune system seen in the postpartum period, when the relative immune suppression of recent pregnancy is no longer present. Women with a history of PPT have a 70% risk of recurrent PPT in a future pregnancy³¹⁵ and should be appropriately counseled if further pregnancies are desired. In longitudinal studies, 10–50% of women in whom the hypothyroid phase of PPT initially resolves will ultimately go on to develop permanent hypothyroidism.^{316,317}

Factors associated with an increased risk of developing permanent hypothyroidism are multiparity, thyroid hypoechogenicity on ultrasound, greater severity of the initial hypothyroidism, serum TPOAb positivity, higher maternal age, and a history of pregnancy loss.^{317,318} PPT can occur following pregnancy loss and in women with pre-existing hypothyroidism, specifically those with Hashimoto's hypothyroidism who do not have a completely atrophic thyroid gland.^{319,320} LT4 given to TPOAb-positive pregnant women at 4–38 weeks' gestation did not change the course of PPT, and LT4 is generally not recommended in this setting for the prevention of PPT.³²¹ Studies regarding selenium supplementation in TPOAb-positive euthyroid pregnant women show mixed results and mostly are of small cohorts in Europe,^{322,323} where background selenium nutrition may be suboptimal^{324,325}; thus, we do not advise routine selenium supplementation for the prevention of PPT. Because of the potential risk of long-term hypothyroidism following PPT, even if LT4 was not required in the hypothyroid phase of PPT, we recommend that women with a history of PPT undergo serum thyroid function testing at one year or upon the development of any hypothyroidism-related symptoms.

Clinical presentation and evaluation. It is important to distinguish between the thyrotoxic phase of PPT and

Graves' disease, given the differences in their natural history and recommended management.^{326,327} The timing of the presentation following birth, biochemical differences, and other clues in the diagnostic evaluation are helpful in differentiating the two entities (Table 9). Serum TRAb and/or TSI positivity, highly specific and sensitive biomarkers of Graves' disease, and a total-triiodothyronine:total-thyroxine ratio of >20³²⁸ are confirmatory for Graves' disease in most cases. In contrast, the onset of thyrotoxicosis in the first six months, shorter duration, and milder signs and symptoms of thyrotoxicosis are more suggestive of PPT. If these factors are not able to determine the etiology, conservative follow-up should be considered, and in severe cases, a thyroid nuclear uptake scan can be considered, although the potential consequences related to breastfeeding (including a decrease in specificity and need to temporarily discard breastmilk during the scan) need to be taken into account.

Although the time course of the phases and the clinical presentation of PPT vary, women may be symptomatic and come to attention during only the thyrotoxic or hypothyroid phase or both. A recommended algorithm for the evaluation and management of postpartum thyroid dysfunction is shown in Flowchart 5. Finally, it should be noted that postpartum depression may arise following PPT in some women, which has been studied in various observational cohorts.^{329–331} Although there is substantial heterogeneity in the available literature and there are overlapping symptoms between the conditions, there appears to be no association between PPT, thyroid autoimmunity, and risk of postpartum depression.^{332–334} If a woman develops depression in the postpartum period, thyroid function testing should be obtained in accordance with general population screening recommendations.



FLOWCHART 5. Approach to abnormal TSH levels in postpartum. Green boxes indicate a diagnosis, yellow boxes indicate an action, and orange boxes indicate recommended follow-up.

Treatment and management. During the thyrotoxic (destructive thyroiditis) phase of PPT, women with hyperthyroid symptoms may be treated with the lowest effective dose of a beta-blocker, which will typically be required for a few weeks. Propranolol and metoprolol are deemed safe in lactation. ATDs should not be used in the treatment of the thyrotoxic phase of PPT, as the underlying mechanism is not increased thyroid hormone production.

Treatment with LT4 for the hypothyroid phase of PPT should be given if the woman has hypothyroid symptoms, breastfeeding, or if she is actively trying for another pregnancy within six months. It should be noted that the benefit of LT4 on breastfeeding outcomes is based on limited data, and breastfeeding should be viewed primarily as a contextual factor that may influence shared decision-making for LT4 use

postpartum, alongside symptom burden, severity of thyroid dysfunction, thyroid autoimmunity, and future pregnancy planning. If LT4 is started for symptomatic control, a trial of tapering or stopping the LT4 should be routinely considered after one year postpartum in women not planning another pregnancy soon, to determine if LT4 is still needed, since the hypothyroid phase of PPT is often transient. If LT4 treatment is not given or delayed during the hypothyroid phase of PPT, serum thyroid function should be rechecked every four to eight weeks until euthyroidism is restored or sustained hypothyroidism necessitates the initiation of LT4; women should be counseled to use adequate contraception until thyroid function has normalized. After a self-limited episode of PPT, the patient can be instructed to seek medical evaluation upon the development of any hypothyroid symptoms.

Other postpartum thyroid dysfunction

Recommendations Table 25: Other Postpartum Thyroid Dysfunction		Strength*	Level #
<i>Management of postpartum hyperthyroidism unrelated to PPT</i>			
The lowest effective dose of ATD in lactation should be used. ^a		Strong	Moderate
Consider applying the same considerations for starting an ATD to women during lactation as those for the general non-pregnant population.		Conditional	Low
If scintigraphy is required during lactation for the diagnostic evaluation of hyperthyroidism, breastmilk should be pumped and discarded for 3–4 days after administering I-123 and 36 hours after administering Tc-99m, before breastfeeding is resumed.		Strong	Low
Do not offer I-131 treatment during lactation. Before I-131 therapy is administered, breastfeeding should be stopped for at least 3 months. A diagnostic I-123 uptake scan may be performed before therapy to assess for mammary iodine uptake, or off-label dopamine agonist therapy may be given to decrease mammary iodine uptake and radiation exposure to mammary tissue.		Conditional	Low
<i>Postpartum follow-up of levothyroxine treatment initiated in pregnancy</i>			
If levothyroxine was started for the treatment of subclinical or mild overt hypothyroidism in pregnancy, a cessation trial may be performed, the timing of which may be determined following shared decision-making. The follow-up frequency and decision to restart levothyroxine may be based on hypothyroid symptoms, thyroid function, TPOAb status, and/or if pregnancy is being planned imminently.		Conditional	Low

^a Doses of up to 20 mg/day of MMI, or 450 mg/day of PTU do not affect newborn thyroid function or neurodevelopment. If lower doses are ineffective, MMI up to 30 mg/day during lactation may be considered in select cases based on the low passage into breast milk

* Strength of Recommendation; # Level of Evidence; Good Practice Statement

PPT, postpartum thyroiditis; ATD, antithyroid drug; TPOAb, thyroperoxidase antibody; MMI, methimazole; PTU, propylthiouracil

Dissenting comments for Recommendations Table 25 from ATA members within the guidelines' writing group are reported in Supplementary Table 3.

The role of thyroid function in breastmilk production and the potential of thyroid dysfunction to affect milk production, duration of lactation, or frequency of lactation are unclear, but clinically relevant adverse effects are unlikely. Some animal studies have reported impaired lactation following the use of PTU, but human data are sparse. There are small studies of deficient lactation in women with hypothyroidism, but these studies either included women already treated with levothyroxine³³⁵ or who had the onset of lactation failure preceding the diagnosis of hypothyroidism.³³⁶ Given the uncertainties around the available evidence, we are unable to recommend for or against screening for thyroid dysfunction in women having difficulty with lactation. Evaluation for Sheehan's syndrome may be considered in case of a lack of breastmilk production after hypotension. Similarly, we are unable to recommend for or against the treatment of hypo- and hyperthyroidism for the strict purpose of improving milk production; in this scenario, lactating women with overt thyroid dysfunction should be treated in accordance with the usual care of nonlactating patients.

Radiopharmaceutical use in lactation. The use of diagnostic radiopharmaceutical agents during lactation should be limited to strict indications, given their proven excretion into human breast milk that would expose the mother to direct radiation to mammary tissue (from increased NIS expression during lactation [Fig. 4]) and the breastfed infant to ingested isotopes from breast milk intake. It should also be noted that the avid RAI uptake directed to breast tissue may impair RAI activity in the thyroid bed and the rest of the body.

Lactating women should stop breastfeeding for 3–4 days (although some groups recommend up to 7 days) after the

administration of ¹²³I and 36 hours after the administration of ⁹⁹Tc pertechnetate.³³⁹ Pertechnetate is generally preferred over ¹²³I due to its shorter half-life. During the temporary stoppage of breastfeeding, all breast milk should be expressed and discarded after the administration of either pertechnetate or ¹²³I. The pumping of breastmilk will increase the biological elimination of the radiopharmaceutical from the breast, decrease overall radiation exposure to the breasts, and facilitate continuation of breastfeeding after scanning. In addition, frequent expression of breast milk will help the mammary gland continue milk production. The woman can be counseled that a reserve of breast milk may be expressed prior to the dosing of the radiopharmaceutical agent, which can be used to feed the nursing infant until she can resume breastfeeding.

¹³¹I therapy has a relatively long half-life (approximately 8 days) and should not be given to lactating women. If there are no other options and ¹³¹I must be considered, the pros and cons of waiting at least three months after cessation of lactation to avoid radiation exposure to the breast should be discussed in a multidisciplinary setting. To aid in the timing of using radiopharmaceuticals (particularly ¹³¹I given its long half-life) for diagnostic scanning and/or treatment, a dopamine agonist to decrease breastmilk production and minimize radiation exposure to the breast may be considered,^{340–344} with the pros and cons of doing so to be discussed in a multidisciplinary setting. Breastfeeding should not resume after ¹³¹I administration.³⁴⁵

Treatment and management of hyperthyroidism during lactation. As radiopharmaceuticals may be useful in the diagnosis and management of hyperthyroidism during lactation, guidance on their administration can be found in the

section immediately above. If ATD treatment of hyperthyroidism is needed during lactation, limited observational and interventional clinical studies show that CMZ doses up to 15 mg/day, MMI doses up to 20 mg/day, and PTU doses up to 750 mg/day (with more robust data for PTU doses up to 450 mg/day) are not associated with thyroid dysfunction in breastfed infants.^{346,347} Breastmilk ATD concentrations are very low compared with maternally ingested doses (for PTU 0.025%, and for MMI 0.14%, of the oral dose).^{348,349} The up to sevenfold difference in breastmilk PTU and MMI concentrations may be related to their pharmacokinetic properties; PTU has greater protein-binding in serum than MMI, characteristics that may potentially inhibit its transfer into lipid-rich breastmilk.³⁵⁰ Only one small study has evaluated infant IQ and neuropsychological measures in breastfed infants of mothers taking ATDs and reported no differences compared with a control group.³⁴⁷ MMI is generally preferred over PTU, due to the risk of PTU-associated hepatotoxicity and the convenience of once-daily dosing. The considerations related to starting ATD treatment for the goal of correcting hyperthyroidism in lactation are generally the same as those outside the lactation setting.³⁴⁶

Finally, potassium iodide may be considered an alternative management option of Graves' disease during lactation, which has been described in iodine-sufficient regions such as Japan. Because iodine is excreted into breast milk and there is a risk of neonatal hypothyroidism, though potassium iodide therapy during breastfeeding requires active infant thyroid function test monitoring.³⁵¹ The pediatrician should be consulted to monitor serum thyroid function if there are clinical signs of thyroid disease in breastfed infants whose mothers have received SSKI within the past two months.

Treatment and management of hypothyroidism during lactation and postpartum period. In women with preexisting hypothyroidism, the increased LT4 dose requirement during gestation is a physiological function of pregnancy itself. Therefore, following delivery, the maternal LT4 dose can generally be reduced to that used prepregnancy, and serum TSH assessed six weeks thereafter. However, adjusting the LT4 to the prepregnancy dose may not be appropriate for all women.³⁵² Women who did not require a full dose of LT4 preconception, or those who have had a considerable weight gain during pregnancy, are more likely to require an LT4 dose that is higher than their preconception dose.

Subclinical hypothyroidism in pregnancy is often transient. Women who were started on LT4 in gestation, especially if the hypothyroidism was mild (i.e., TSH <6 mU/L), may be offered a trial of tapering or discontinuing LT4 (particularly if the dose is ≤75 mcg/day) shortly after delivery. Alternatively, this trial may also be deferred until after the initial newborn period, when there is likely less baseline fatigue. Should LT4 be discontinued or its dose decreased postpartum, serum TSH should be evaluated in approximately six weeks.³⁵³ Pooled data from two randomized controlled trials have reported a 13.5% and 15.6% incidence of overt hypothyroidism when women who had subclinical hypothyroidism at 8–20 weeks'

gestation were universally screened for thyroid dysfunction at 1 and 5 years postpartum, respectively.³¹³

J. Future Research Directions

In the 2017 version of these guidelines, there were 13 suggested research directions, from which new data have considerably impacted the current guidelines for 4 of these. Below are the updated suggested research directions:

1. Further studies to determine risk-based reference intervals for thyroid function tests in pregnancy.
2. Studies assessing the cost-effectiveness of thyroid function and thyroid antibody screening in women with a history of miscarriage or infertility.
3. Studies assessing clinical (preconception) risk factors for thyroid disease during pregnancy.
4. A comprehensive study to assess the iodine status of pregnant and lactating women in the United States.
5. Studies to determine safe upper limits for iodine ingestion in pregnancy and lactation.
6. Studies quantifying the risk of subfertility, success of fertility treatment, and/or progression to overt thyroid disease during pregnancy in women with preconception subclinical thyroid dysfunction or thyroid autoimmunity.
7. A randomized trial of early LT4 intervention (preconception or early pregnancy, i.e., 6–10 weeks' gestation) in women with either subclinical hypothyroidism or isolated hypothyroxinemia to determine effects on adverse pregnancy outcomes and child IQ.
8. Studies assessing the effect of LT4 on adverse pregnancy outcomes in different subgroups of euthyroid TPOAb-positive women to establish potential intervention strategies.
9. Prospective studies on the risk of adverse pregnancy and offspring outcomes for women with active Graves' disease during pregnancy.
10. Studies on serum (f)T3 and (f)T4 monitoring target concentrations in women with Graves' disease treated with ATD.
11. Studies evaluating the safest timing of administration of different ATDs for management of hyperthyroidism in pregnancy.
12. Studies assessing novel ways to differentiate fetal hyperthyroidism from fetal hypothyroidism when a fetal goiter is detected.
13. Studies investigating the impact of postpartum and pre-existing thyroid dysfunction on lactation.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3

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