Ata guidelines 2017 pregnancy

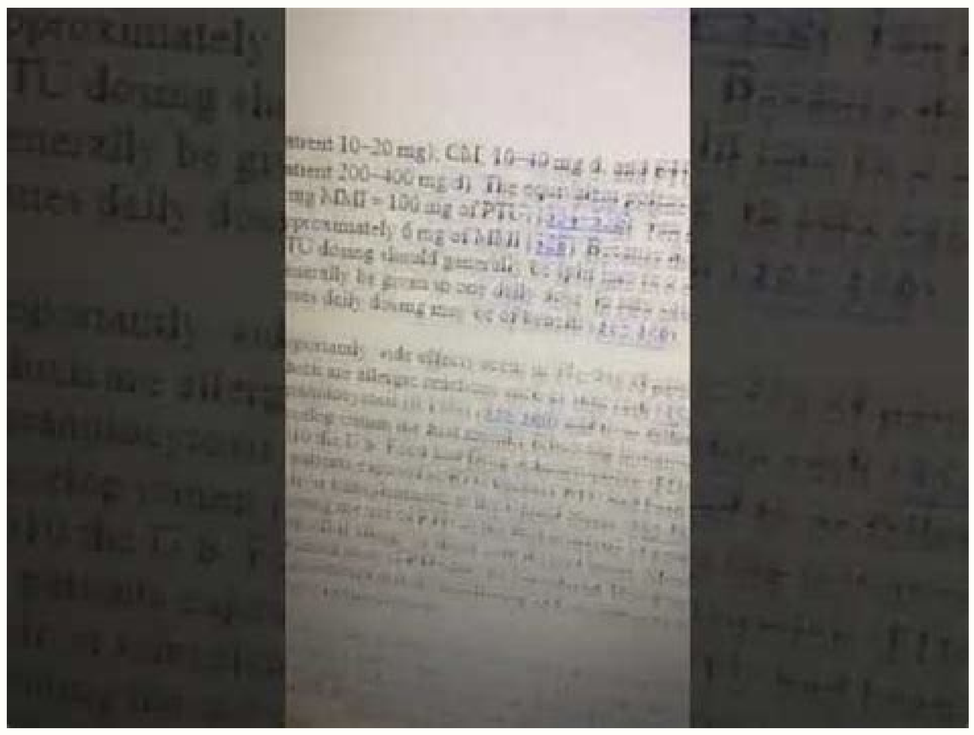
I'm not robot!

Introduction (cont..)

- By 2019, one study predicts that papillary thyroid cancer will become the third most common cancer in women at a cost of 19-21 billion dollars in the U.S.
- The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer, which occurs in 7%–15% of cases depending on age, sex, radiation exposure history, family history, and other factors.

Thyroid sonography (cont…)

- Sonography features that are associated with thyroid cancer include:
  - microcalcifications,
  - nodule hypoechogenicity compared with the surrounding thyroid or strap muscles,
  - irregular margins (defined as either infiltrative, microlobulated or spiculated), and
  - A shape taller than wide measured on a transverse view.



Sonographic Pattern	Features	Risk of Malignancy	Biopsy when:
High Suspicion	**Hypoechoic solid** and at least one of: - irregular margin - microcalcifications - taller than wide - rim calcification with soft tissue extrusion - extrathyroid extension	70-90%	≥1 cm (< 1cm if extrathyroid extension or suspicious lymph nodes)
Intermediate Suspicion	**Hypoechoic solid** without suspicious features	10-20%	≥1 cm
Low Suspicion	- Isoechoic or hyperechoic solid - Partially cystic with eccentric solid component	5-10%	≥1.5 cm
Very Low Suspicion	- Spongiform - Partially cystic without eccentric solid component	<3%	≥2 cm (observation also appropriate)
Benign	- Cystic	<1%	Never

Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.

Criteria for the diagnosis of diabetes

FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

2017 ata guidelines thyroid pregnancy. Ata guidelines for healthy pregnancy. Ata guidelines in pregnancy.

Pregnancy is a complex endocrinologic and immunologic process that has wide-reaching effects on thyroid hormone homeostasis. Increased estrogen levels result in a 50% elevation of thyroxine binding globulin with a concomitant 50% increase in total thyroxine (TT4) and triiodothyronine. Placental production of human chorionic gonadotropin (hCG) drives a decrease in the thyroid stimulating hormone (TSH) upper limit of normal due to cross reactivity of hCG at the TSH receptor. These critical adaptations in pregnancy are necessary for a healthy pregnancy and a healthy baby. However, the normal physiological changes in thyroid hormone levels make it difficult to distinguish between normal and abnormal hormonal values. The ability to accurately diagnose thyroid hormone abnormalities has increased in importance over the last two decades as ongoing research has linked thyroid hormone disturbances to miscarriage, preterm delivery, gestational hypertension, gestational diabetes, preeclampsia and decreased IQ in the offspring (1). Clinical guidelines published by national and international societies help providers diagnose and treat thyroid disease in pregnancy. In 2011, the American Thyroid Association (ATA) published comprehensive Guidelines on Thyroid Disease During Pregnancy and the Postpartum (ATA Guidelines), covering more than 20 years of published literature from 1990 up to 2011, along with seminal works pre-dating 1990 (2). Upon release of the 2011 ATA Guidelines, the goal was for a revision to occur within 4–5 years of publication. Nevertheless, new guidelines, which included studies up to the guideline publication date, were not published by the ATA until March of 2017 (3). During that interval, the literature in the field increased rapidly. Specifically, the 2017 ATA Guidelines included citations to 621 references, nearly doubling the 319 references cited in 2011 (2, 3). Thyroid and pregnancy research continues to be published at a rapid pace. A Pubmed search on “thyroid and pregnancy” reveals over 500 articles that were published in 2017 and 2018. An increasing number of interventional trials are ongoing, promising to yield critical data on the impact of levothyroxine (LT4) therapy in pregnant women with subclinical hypothyroidism and euthyroid autoimmune thyroid disease. It is apparent that a 6-year cycle between Guidelines is too lengthy in which to keep providers up to date. Guideline generation needs to change from a static document to a dynamic document which quickly responds to the publication of new, high-quality research. In a 2014 systematic review of methodological handbooks for clinical practice guideline development, Vernooij et al. concluded that the optimal timeframe between publication of a guideline and the start of an updating process was 2–3 years (4). Based on this conclusion, the updating process for the next version of the ATA Guidelines should already be well under way. Calls for dynamic guidelines have also been made, and platforms for such guidelines are available (5, 6). For example, the 2017 Canadian Guidelines on Opioids for Chronic Non-Cancer Pain were made available on the digital MAGICapp platform, allowing for dynamic updates in real time as the field evolves (7). Objectives A methodology for dynamically updating guidelines on thyroid disease in pregnancy need to be developed. In fact, we predict that dynamic guidelines will soon become the norm. In the interim, it is important to analyze the thyroid and pregnancy literature published since the 2017 Guidelines. Specifically, the present article synthesizes the publications in two of the more controversial areas in the field of thyroid and pregnancy, namely hypothyroidism and thyroid autoimmunity. The results from the literature published in calendar years 2017 and 2018 will be placed in the context of the 2017 ATA Guideline Recommendations. Research Question How does the increased rate of publications in the field of thyroid disease in pregnancy impact the state of current clinical guidelines? Methods Study Design, Search Strategy and Review Protocol This study is conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (8). One author (AD) carried out a literature search using the Pubmed database on 1/2/2019 using the terms “thyroid” and “pregnancy.” All studies with a publication date from 1/1/2017 to 12/31/2018 were identified and imported into RefWorks 2.0 (ProQuest, Ann Arbor, MI) where duplicates were removed. Titles and abstracts were scanned to categorize articles by subject using the subject headings of the 2017 ATA Guidelines (3). Case reports, commentaries, corrections and both narrative and systematic reviews were excluded. Articles in the categories of “Hypothyroidism and Pregnancy” and “Thyroid Auto-Antibodies and Pregnancy Complications” were reviewed in full-text by two authors (AD and AS-G). Study design and results were extracted from all articles by one author (AD). Using the published questions and recommendations in the 2017 ATA Guidelines (3), relevant articles were grouped and synthesized in this review. A flow diagram for study selection is shown in Figure 1. A list of full-text excluded articles with reasons for exclusion can be found in Supplemental Table 1. Figure 1. Prisma flowchart depicting article selection strategy. Articles were selected based on relevance to existing ATA recommendations or perceived need for new recommendations. Given the heterogeneous nature and designs of the studies included in this review, a formal, tool-based risk of bias assessment was not carried out. However, all included studies are discussed in detail within the text of this review along with any perceived limitations to their designs. Results Hypothyroidism Sixty-six original studies were published on hypothyroidism in pregnancy since the publication of the 2017 ATA Guidelines. For this review, 26 original research studies on the effects of overt hypothyroidism, subclinical hypothyroidism and isolated hypothyroxinemia on pregnancy outcomes and treatment in pregnancy met inclusion criteria based on relevance to existing questions or recommendations posed in the 2017 ATA Guidelines. a) Adverse Outcomes of Overt Hypothyroidism (Question 33) “What adverse outcomes are associated with overt hypothyroidism during pregnancy?” Four studies were published since the 2017 ATA Guidelines that included women who were clearly overtly hypothyroid (9–12). Three out of the four studies found at least one adverse outcome associated with overt hypothyroidism (9–11). In a retrospective cohort study of 1,153 mother-child pairs from the Danish National Birth Cohort, Andersen et al. reported an association between overt hypothyroidism and lower child verbal IQ, with children born to mothers with TSH ≥10 having an average 8.9 point reduction, CI −15 to −2.4, in verbal IQ score compared to children born to mothers with a TSH of 0.1–2.49 mIU/L (9). Andersen et al. also published a case-cohort study of 7,624 pregnant women from the Danish National Birth Cohort, finding an association between maternal overt hypothyroidism and epilepsy in their children, aHR 3.5, CI 1.2–10 (10). In a prospective study of 1,082 Chinese women, Yang et al. found a significant association between overt hypothyroidism and preterm delivery with 15.4% (2/13) of mothers with overt hypothyroidism having a preterm delivery compared to 3.5% (31/882) of euthyroid mothers, aOR 8.99, CI 1.73–46.77 (11). On the other hand, Nelson et al. in a prospective study of 4,615 mother-child pairs, found no association between overt hypothyroidism and child educational attainment, with children from overtly hypothyroid mothers displaying no statistical difference in the number of A*/A grades received compared to those from euthyroid mothers, OR 0.25, CI 0.05–1.17, number of courses passed at any grade level, RR 0.95, CI 0.80–1.12, or number of courses attempted, Ratio of Geometric Means (RGM) 1.04, CI 0.92–1.18 (12). Two other studies included women that were labeled as “hypothyroid” without specification to overt vs. subclinical disease; however, these women were “likely” overtly hypothyroid based on the context of the studies (13, 14). Both of these studies found a link between hypothyroidism and adverse outcomes. In a population-based cohort study of 595,669 Danish children from the Danish national registry, Liu et al. (13) found a significant association between diagnosed maternal hypothyroidism during pregnancy that required eventual treatment and asthma development in children, IRR 1.16, CI 1.03–1.30. Children from mothers that did not receive treatment had an even higher risk of developing asthma, IRR 1.37, CI 1.04–1.80 (13). Jølving et al. (14) reported in a retrospective cohort study of 1,560,955 Danish children of whom 2,618 were born to mothers with Hashimoto's thyroiditis. The authors reported that the children born to women with Hashimoto's thyroiditis were more likely to develop thyroid disease themselves compared to children born to mothers without Hashimoto's thyroiditis, 2.2% (58/2,618) vs. 0.3% (4,404/1,557,577), aHR 12.83, CI 9.74–16.9. There was also an increased risk of type 1 diabetes in children born to mothers with Hashimoto's thyroiditis, 0.6% (15/2,618) vs. 0.3% (5,106/1,557,577), aHR 2.47, CI 1.46–4.18 (14). The 2017 ATA Guidelines conclude that there is a “clear association between overt maternal hypothyroidism and risk to the maternal-fetal unit,” specifically resulting in an increased risk of preterm delivery, low birth weight, miscarriage, and impairment of neurocognitive development their children (3). The studies reviewed above continue to find significant associations between maternal overt hypothyroidism and impaired offspring neurocognitive development and preterm delivery, as well as suggesting an increased risk of childhood asthma, thyroid disease and type I diabetes, confirming the association between maternal overt hypothyroidism and adverse maternal/fetal events. b) Adverse Outcomes of Subclinical Hypothyroidism (Question 34) “What adverse outcomes are associated with subclinical hypothyroidism during pregnancy?” Ten studies on adverse outcomes in subclinical hypothyroidism have been published in 2017 and 2018 as noted in Table 1 (9–12, 15–21). Two studies reported that subclinical hypothyroidism was associated with changes in fetal growth, however, the changes were different between studies (15, 16). In an observational cohort study of 3,988 Dutch women from the Amsterdam Born Children and Their Development (ABCD) cohort, Vrijkotte et al. found an increased risk of males being born large for gestational age in women with subclinical hypothyroidism compared to those born to women without subclinical hypothyroidism, OR 1.95, CI 1.22–3.11 (15). In a cross-sectional study of 3,832 women from the Proteomics in Pre-Eclampsia study, Carty et al. found that women with a TSH >5 mIU/L delivered lower birthweight babies than those who had a TSH 2.5 mIU/L had a delivery prior to 34 weeks, as did 2.7% (11/404) of those with a TSH >4.0 mIU/L, compared to 1.2% (38/3,231) of euthyroid controls, P = 0.035 (20). In the prospective study by Yang et al. subclinical hypothyroidism was found to be associated with preterm delivery compared to euthyroid controls; 10.5% (4/38) vs. 3.5% (31/882), aOR 4.58, CI 1.46–14.4 (11). In a prospective study, Nassie et al. (17) compared 117 Israeli women presenting with preterm uterine contractions to 134 women without preterm uterine contractions. No significant difference was found between the prevalence of subclinical hypothyroidism in women with or without preterm contractions, 37% (43/117) vs. 46% (62/134), P = 0.13. However, the authors reported that subclinical hypothyroidism was significantly more prevalent in women with a history of prior preterm delivery. Of the 34 women with a history of preterm delivery, 62% (21/34) had subclinical hypothyroidism, compared to 41% (84/207) of women without a history of preterm delivery, P = 0.017 (17). Lastly, in an observational cohort study of 5,644 thyroid peroxidase antibody (TPOAb) negative women from the Dutch Generation R cohort, Korevaar et al. found that women with elevated TSH levels with higher hCG levels had a higher risk of preterm delivery and preterm premature rupture of membranes, but those who had lower levels of hCG did not, suggesting that risk of adverse events from subclinical hypothyroidism may be modified based on levels of hCG (21). One study reported no significant association between subclinical hypothyroidism and pregnancy loss in women with unexplained recurrent pregnancy loss. In this retrospective study of 317 Japanese women with unexplained recurrent pregnancy loss, Uchida et al. found that among women with untreated “borderline” subclinical hypothyroidism, defined as a TSH between 2.5 and 4.5 mIU/L, 29% (9/31) had a subsequent pregnancy loss compared to 17.9% (24/134) of euthyroid controls, P = 0.16 (18). One study reported an association between maternal subclinical hypothyroidism and neurodevelopmental conditions in their children. In this case-cohort study by Andersen et al. an increased risk of autism spectrum disorder (ASD) was noted, HR 1.70, CI 1.04–2.75, though no association was found between subclinical hypothyroidism and epilepsy, HR 1.04, CI 0.61–1.77 or attention deficit hyperactivity disorder (ADHD), HR 1.06, CI 0.76–1.48 (10). Two studies on neurodevelopmental conditions in children of mothers with subclinical hypothyroidism found no significant association (9, 12). In the retrospective study from the Danish National Birth Cohort by Andersen et al. no association was found between subclinical hypothyroidism, defined as a TSH from 2.5 to 9.99 mIU/L, and offspring verbal IQ (9). In the prospective study by Nelsen et al. no association was found between subclinical hypothyroidism and A/A* grades, passing grades or courses attempted, OR 1.02, CI 0.58–1.17; RR 1.02, CI 0.80–1.12; and RGM 1.02, CI 0.92–1.18, respectively (12). One other study reported mixed results in regards to subclinical hypothyroidism and perinatal outcomes. In a retrospective study of 745 Japanese women, Furukawa et al. (19) found a significantly higher rate of gestational diabetes in women with subclinical hypothyroidism, 6% (10/167) vs. 0.3% (2/578) of controls, P < 0.01. However, in an analysis of composite rates of adverse outcomes including placental abruption, gestational diabetes, hypertension, stillbirths, babies large and small for gestational age or having low 5 min Apgars, there was no significant difference between the two groups, 14% (23/167) in women with subclinical hypothyroidism vs. 16% (92/578) of controls, P = 0.50 (19). The 2017 ATA Guidelines concluded that the evidence indicated “an increasing risk of pregnancy-specific complications, most notably pregnancy loss and preterm delivery, in relation to elevated maternal TSH concentrations” (3). The articles published in 2017 and 2018 support the 2017 ATA Guidelines' conclusion on an association between subclinical hypothyroidism and preterm delivery. The reported association appears more pronounced when subclinical hypothyroidism is defined as a TSH of 4.0 mIU/L or above, or a population-based reference value, compared to using 2.5 mIU/L or above. The association between subclinical hypothyroidism and adverse neurocognitive outcomes appears less clear. Of the three studies published on these outcomes since the 2017 ATA Guidelines, only Andersen et al. (9, 10) reported a weak association between subclinical hypothyroidism and ASD. Thus, taken as a whole, it would appear that subclinical hypothyroidism is associated with preterm delivery; however, the

association with offspring neurocognitive outcomes remains controversial. Of note, the vast majority of published studies did not take into account thyroid autoimmune status in their findings. Thus, it remains difficult to draw conclusions on the effect modification thyroid autoimmunity may have on the impact of subclinical hypothyroidism on perinatal and neonatal outcomes. c) Treatment of Subclinical Hypothyroidism (Question 37) “Should women with subclinical hypothyroidism be treated in pregnancy?” and (Recommendation 29) LT4 therapy is recommended for TPOAb-positive women with elevated TSH and TPOAb-negative women with a TSH >10.0 mIU/L; LT4 therapy may be considered for TPOAb-positive women with TSH >2.5 mIU/L or TPOAb-negative women with elevated TSH; LT4 therapy is not recommended in TPOAb-negative women with normal TSH Five studies published since the 2017 ATA Guidelines addressed the treatment of subclinical hypothyroidism in pregnancy (22–26). Two studies reported a decrease in negative perinatal outcomes in women who were treated (22, 23). In a prospective study of 93 women with subclinical hypothyroidism, defined as TSH above 2.5 mIU/L in the first trimester or above 3.0 mIU/L in the second trimester, Zhao et al. (22) found a significant decrease in overall pregnancy complications, including gestational hypertension, preeclampsia, anemia and/or gestational diabetes in women treated at 8–10 weeks gestation compared to those treated at 13–16 weeks gestation or those who went untreated; 10% (3/31) vs. 41.9% (13/31) vs. 64.5% (20/31), respectively, P < 0.01. Similarly, rates of at least one pregnancy complication, including preterm labor, pregnancy loss, postpartum hemorrhage, or low birth weight, was decreased with early treatment of subclinical hypothyroidism, 3.2% (1/31) vs. 32.3% (10/31) vs. 38.7% (12/31), respectively, P = 0.03 (22). In a randomized controlled trial of 366 TPOAb negative Iranian women with subclinical hypothyroidism, defined as a TSH above 4.0 mIU/L, Nazarpour et al. found a significantly lower rate of preterm delivery in women who received levothyroxine compared to untreated women, RR 0.38, CI 0.15–0.98 (23). Two studies reported no benefit of treatment (24, 25). In a randomized controlled trial of 677 women, Casey et al. found no benefit of levothyroxine intervention at an average 16.7 weeks gestation compared to placebo in women with subclinical hypothyroidism, defined as TSH above the 97.5th percentile, for either IQ at 5 years of age, 97 vs. 95, P = 0.89, or for adverse pregnancy outcomes, including preterm delivery, 9% (31/339) vs. 11% (37/339), P = 0.44; preeclampsia, 6% (22/339) vs. 6% (22/338), P = 0.76; gestational diabetes, 7% (25/339) vs. 7% (22/338), P = 0.66; miscarriage 1% (4/339) vs. 2% (7/339), P = 0.36; and low birth weight, 10% (33/339) vs. 8% (27/338), P = 0.45 (24). In the 5-year follow up study of 4,609 women-child pairs from the 2012 Antenatal Thyroid Screening and Childhood Cognitive Function study, Hales et al. found no difference between the number of children with IQ 0.05 (37). The 2017 ATA guidelines conclude that, “the data for an association between thyroid antibodies and recurrent pregnancy loss are less robust than for sporadic loss.” The study by Cueva et al. (37) supports this statement. However, the presence or absence of an association remains an open question, and additional studies will be required to fully answer this question. c) Autoimmunity and Preterm Delivery (Question 19) “Is there an association between thyroid autoantibody positivity and premature delivery?” Four studies examined the association between thyroid autoimmunity and preterm delivery (34, 38–40), three of which were positive (34, 38, 40). In the study by Rajput et al. TPOAb positive women had a significant increase in preterm delivery compared to TPOAb negative women, 14% (21/150) vs. 3.3% (5/150), respectively, P = 0.001 (34). In a large prospective cohort study of 2,931 Chinese women, Han et al. reported a significant association between thyroid antibody positivity in the second trimester, but not the first trimester and preterm delivery, OR 1.863, CI 1.009–3.411, and, OR 1.513, CI 0.869–2.633, respectively (38). In an individual participant data meta-analysis of 11,212 women from three cohorts, the Generation R, ABCD and the Holistic Approach to Pregnancy (HAPPY) cohorts, Korevaar et al. (40) reported a significant dose-dependent relationship between TPOAb titers modified by TSH concentrations and premature delivery, P = 0.05 for TSH X log(TPO) interaction. This was true even for women with antibody levels considered negative by manufacturer cutoffs, especially if they also had higher levels of TSH (40). Further studies will be needed to investigate this finding. One study found no association between thyroid autoimmunity and preterm delivery. In a secondary analysis of the EAGeR (Effects of Aspirin in Gestation and Reproduction) randomized, placebo-controlled trial in which 1,193 women with 1–2 prior pregnancy losses were prescribed low dose aspirin or placebo, Plowden et al. found no association between thyroid antibodies and preterm delivery, aRR 1.26, CI 0.65–2.45 (39). The 2017 ATA guidelines conclude that “thyroid auto-antibody positivity is associated with increased risk for preterm delivery” (3). Based on the results of the four studies published since the 2017 ATA Guidelines, this statement is still appropriate, but further investigation is warranted. d) Treatment of euthyroid autoimmunity (Question 18 and Recommendation 14) “Does treatment with LT4 or intravenous immunoglobulin therapy decrease the risk for pregnancy loss in euthyroid women with thyroid autoimmunity? and (Question 20 and Recommendation 15) “Does LT4 treatment of euthyroid women who are thyroid autoantibody positive reduce risk for premature delivery?” One study since the 2017 ATA guidelines examined the impact of levothyroxine on miscarriage and preterm delivery in women with thyroid autoimmunity (45). In an Iranian randomized controlled trial comparing 56 LT4 treated, TPOAb positive women to 58 untreated, TPOAb positive women, Nazarpour et al. (45) reported a significantly lower rate of preterm delivery in treated TPOAb positive women compared to those who went untreated, 7.1% (4/56) vs. 23.7% (14/58), P < 0.001. There was no significant reduction in rates of miscarriage however, 3.6% (2/56) vs. 3.4% (2/54), P > 0.05 (45). This study by Nazarpour, however, included both euthyroid and subclinically hypothyroid women. In a subgroup analysis stratifying by TSH > 4 mIU/L, only treated women with TSH > 4 mIU/L showed benefit of treatment, with 5.3% (2/38) of treated women delivering preterm compared to 29.4% (10/34) of untreated women, P = 0.01. Women with TSH 0.05 (42). The 2017 ATA Guidelines were inconclusive on an association between thyroid antibody positivity and placental abruption, postpartum depression, and neurocognitive development (3). The literature since the 2017 ATA Guidelines add no new findings on these associations but do report a negative association between thyroid autoimmunity and preeclampsia (39), and a positive association between thyroid antibodies and gestational diabetes in one study (41), but no association in two others (39, 42). Based on this recent literature, there does not appear to be a link between thyroid antibodies and preeclampsia and the relationship between thyroid antibodies and gestational diabetes remains inconclusive; however, further investigation is warranted for both these outcomes. The two studies on childhood risk for metabolic syndrome and on childhood IQ raise intriguing questions regarding the long-term impact of thyroid antibodies on offspring development (43, 44). At present, the findings from these two studies should be considered preliminary and require confirmation. Based on the studies published since the 2017 ATA Guidelines, no alteration of the Guidelines are indicated, but further investigation is warranted. f) Autoimmunity and Assisted Reproductive Technologies (Question 28) “Is maternal antithyroid Ab positivity associated with poorer outcomes following ART?” Five studies examined the association between thyroid autoimmunity and outcomes of ART (46–50). Two studies reported a negative association between thyroid autoimmunity and outcomes after ART (48–50). In a retrospective cohort study of 300 Turkish women with diminished ovarian reserve undergoing in-vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), Beydilli Nacak et al. found that TPOAbs were significantly associated with “poor cycle outcome,” RR 2.8 CI 1.2–6.3 (48). In another case-control study of 52 Greek women undergoing IVF or IVF/ICSI, 26 with thyroid antibodies and 26 matched-controls, Medenica et al. reported significantly lower pregnancy rates per cycle in women with thyroid antibodies, 31% vs. 62%, P = 0.026 (exact cycle numbers not available), as well as significantly lower pregnancy rates per embryo transfer, 35 vs. 67%, P = 0.029 (exact transfer numbers not available) (50). However, three studies reported no difference in ART outcomes between women with and without thyroid autoimmunity (46, 47). In a retrospective cohort study of 3,143 euthyroid patients undergoing intrauterine insemination (IUI), among the 376 women who went on to conceive, Unuane et al. reported no difference in live birth rates between TPOAb positive and TPOAb negative women, 86% (19/22) vs. 82% (201/354), respectively, OR 1.05, CI 0.76–1.47 (46). In a retrospective cohort study of 123 infertile, euthyroid women undergoing IVF or IVF with ICSI, 29 with thyroid autoimmunity and 94 without, Andrisani et al. also reported no difference in implantation rates, 15 vs. 19%, P > 0.05 (exact cycle numbers not available), pregnancy rates, 29 vs. 34%, P > 0.05 (exact cycle numbers not available) or ongoing pregnancy rates, 26 vs. 31%, P > 0.05 (exact cycle numbers not available), although they did report significantly fewer grade 1 embryos collected in patients with antibody positivity, 22% (26/119) vs. 45% (176/394), P < 0.001 (47). In a case-control study of 46 Chinese women undergoing IVF with fresh embryo transfer, 19 with TPOAbs and 27 without, Lu et al. reported no difference between women with and without TPOAbs in the implantation rate, 21% (8/38) vs. 32% (17/53), P = 0.25 and clinical pregnancy rate, 42% (8/19) vs. 52% (14/27), P = 0.51 (49). The 2017 ATA Guidelines came to no conclusion regarding the impact of thyroid autoimmunity on ART outcomes given the mixed data available at the time (3). The studies published since the 2017 ATA Guidelines are similarly discordant. Thus, no changes to the Guidelines are warranted based on this recently published research; however, further investigation is warranted. Studies involving ART and thyroid autoimmunity suffer from differences in populations and ART protocols making aggregation of data difficult. Of note, a 2018 meta-analysis by Poppe et al. (51) noted that miscarriage rates in thyroid autoantibody positive women undergoing ART have been declining in contemporary studies compared to in studies reported in the past. The authors hypothesize that this may be due to the increase in rates of intracytoplasmic sperm injection (ICSI), which may disproportionally benefit women with thyroid autoimmunity (51). Thus, better quality studies that isolate specific ART methodologies will be needed to fully answer this question. g) Treatment of Thyroid Autoimmunity in ART (Question 29) “Does treatment of antithyroid Ab-positive euthyroid women improve ART outcomes?” and (Recommendation 21) “Insufficient evidence exists to determine whether LT4 therapy improves the success of pregnancy following ART in TPOAb-positive euthyroid women.” There has been one study published since the 2017 ATA Guidelines which evaluated treatment of euthyroid, thyroid antibody positive women undergoing ART. In an open-label, randomized trial, Wang et al. (52) compared 300 euthyroid, TPOAb positive women undergoing IVF who received levothyroxine daily, 25 μg daily for TSH /=2.5mU/l in early pregnancy: Prevalence and subsequent outcomes. Eur J Obstet Gynecol Reprod Biol. (2017) 210:366–9. doi: 10.1016/j.ejogrb.2017.01.048 PubMed Abstract | CrossRef Full Text | Google Scholar 17. 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