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Assessment and treatment of thyroid disorders in pregnancy and the postpartum period

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Abstract

Thyroid disorders are prevalent in pregnant women. Furthermore, thyroid hormone has a critical role in fetal development and thyroid dysfunction can adversely affect obstetric outcomes. Thus, the appropriate management of hyperthyroidism, most commonly caused by Graves disease, and hypothyroidism, which in iodine sufficient regions is most commonly caused by Hashimoto thyroiditis, in pregnancy is important for the health of both pregnant women and their offspring. Gestational transient thyrotoxicosis can also occur during pregnancy and should be differentiated from Graves disease. Effects of thyroid autoimmunity and subclinical hypothyroidism in pregnancy remain controversial. Iodine deficiency is the leading cause of hypothyroidism worldwide. Despite global efforts to eradicate iodine deficiency disorders, pregnant women remain at risk of iodine deficiency due to increased iodine requirements during gestation. The incidence of thyroid cancer is increasing worldwide, including in young adults. As such, the diagnosis of thyroid nodules or thyroid cancer during pregnancy is becoming more frequent. The evaluation and management of thyroid nodules and thyroid cancer in pregnancy pose a particular challenge. Postpartum thyroiditis can occur up to 1 year after delivery and must be differentiated from other forms of thyroid dysfunction, as treatment differs. This Review provides current evidence and recommendations for the evaluation and management of thyroid disorders in pregnancy and in the postpartum period.

Thyroid disorders are fairly common in women of reproductive age. Hashimoto thyroiditis and Graves disease, both autoimmune thyroid disorders, are eight to ten times more frequent in women than in men and have a peak prevalence in early adulthood[1]. Of note, hypothyroidism is estimated to occur in 4% of pregnancies (0.5% overt and 3.5% subclinical hypothyroidism) and hyperthyroidism in 2.4% of pregnancies (0.6% overt and 1.8% subclinical hyperthyroidism)[2]. Thyroid hormone is important for both maternal and child health. Although the fetal thyroid gland is present and functional by 10–12 weeks gestation, it does not mature until 18–20 weeks[3]. Thus, the fetus depends on maternal thyroid hormone delivered via transplacental passage during a critical period of development in early gestation[3]. Consequently, maternal thyroid dysfunction can lead to

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adverse pregnancy and child neurodevelopmental outcomes. In addition, in the postpartum period, ~5% of women might experience transient thyroid dysfunction from postpartum thyroiditis within 12 months of delivery[4].

Human chorionic gonadotropin (hCG), a hormone produced by the placenta during pregnancy, has a weakly thyrotrophic effect[5] and can promote the development and growth of thyroid nodules in pregnancy. The prevalence of thyroid nodules in pregnancy has been reported to be as high as 29%, depending on the iodine status of the population studied[6,7]. Of note, a worldwide increase has occurred in the incidence of thyroid cancer in young women in the past few decades. Thyroid cancer is now the most common type of cancer diagnosed in women aged 15–29 years and the second most common type in women aged 30–39 years[8–10].

In this Review, we present current evidence regarding the diagnosis and management of thyroid disorders during pregnancy and the postpartum period. We note that unless otherwise specified, the term ‘women’ refers to ciswomen, as the research highlighted in this Review included only ciswomen. There is currently a lack of available research regarding thyroid disease in pregnancy in transmen and non-binary pregnant people.

Thyroid dysfunction in pregnancy

Assessment of thyroid hormone levels in pregnancy

During pregnancy, the weakly thyrotrophic effect of hCG on the thyroid gland increases thyroid hormone production (FIG. 1), which in turn decreases thyroid stimulating hormone (TSH) secretion from the pituitary gland via negative feedback[11]. Thus, in early pregnancy when levels of hCG are high, serum levels of TSH tend to shift downwards compared with those of non-pregnant adults[12]. Serum levels of TSH typically increase slightly after the first trimester, largely due to a decrease in serum levels of hCG[11]. The levels of thyroid hormone in pregnancy can differ by race and/or ethnicity, and iodine status of populations. Therefore, the American Thyroid Association (ATA) and the American College of Obstetricians and Gynecologists (ACOG) recommend using population-specific, assay-specific and trimester-specific ranges for thyroid function tests in pregnant women[6,13]. If such ranges are not available, a TSH reference range of 0.1–4.0 mIU/l can be used in early gestation (for context, the reference range for non-pregnant adults is usually 0.5–4.5 mIU/l)[6,13].

Serum TSH should be used as the initial screening test for thyroid dysfunction in pregnancy, as TSH is the most sensitive marker for primary thyroid dysfunction. In addition, serum levels of free T_4 can be used to distinguish between overt and subclinical thyroid dysfunction. Overt hypothyroidism is defined by high serum levels of TSH with low levels of free T_4, whereas in subclinical hypothyroidism serum levels of TSH are elevated but levels of free T_4 are normal. Similarly, women with overt hyperthyroidism have low serum levels of TSH with elevated levels of free T_4 and those with subclinical hyperthyroidism have low serum levels of TSH with normal levels of free T_4.

Accurate measurement of serum levels of free T_4 is challenging in pregnant women. High levels of oestrogen in pregnancy cause a twofold increase in serum levels of thyroxine-

binding globulin (TBG)[14]. Indirect free T_4 immunoassays can be confounded by high TBG, which can lead to falsely low results, especially in the second and third trimesters of pregnancy. The free T_4 index, which utilizes assessment of levels of total T_4 and an index of binding to calculate free T_4, might be more accurate than indirect immunoassays in high TBG states such as pregnancy[15]. In 2018, Gronowski argued that the decrease in serum levels of free T_4 measured by immunoassay seen in the second and third trimesters of pregnancy might be physiological[16]. Furthermore, a 2021 study in about 300 euthyroid pregnant Spanish women showed that serum levels of free T_4 (measured by two different immunoassays) decreased in the second and third trimesters[17]. Whether the decrease in free T_4 observed in the second and third trimesters is actually physiological remains to be confirmed. Although levels of free T_4 measured by immunoassays correlated well with levels of free T_4 measured by liquid chromatography with tandem mass spectrometry (LC–MS–MS) in the first trimester, the reference ranges were not interchangeable at any time point and the immunoassay results were not correlated with LC–MS–MS results in the second and third trimesters. Serum levels of free T_4 measured by LC–MS–MS remain the gold standard for assessing levels of free thyroid hormone, but this technique is cumbersome and expensive. Although the modern immunoassays for free T_4 measurements might be more reliable than older immunoassays in pregnancy, the pregnancy-specific, trimester-specific reference ranges for each assay are needed. If a reliable assay for free T_4 or the free T_4 index is not available, levels of total T_4 or total T_3 can be used as surrogates for the measurement of free hormone. Of note, between 7 and 16 weeks gestation, the non-pregnancy assay reference ranges for total T_4 or T_3 can be increased by 5% per week to account for rises in serum levels of TBG. When serum levels of TBG stabilize beyond 16 weeks gestation, 150% of the upper limit of non-pregnant reference ranges for total T_4 and T_3 levels can be used[18].

Hypothyroidism in pregnancy

Overt hypothyroidism and obstetric outcomes.—The adverse obstetric and perinatal effects of maternal overt hyperthyroidism have been well documented. For example, increased rates of gestational hypertension (that is eclampsia, pre-eclampsia and pregnancy-induced hypertension), placental abruption, postpartum haemorrhage, preterm delivery, low birthweight and fetal death were initially reported in women with overt hypothyroidism and their infants in the 1980s to the 1990s[19,20]. More recently, a 2013 US national cohort study including 223,512 pregnant women similarly showed that untreated maternal overt hypothyroidism increased the risks of pre-eclampsia, gestational diabetes mellitus, preterm birth, caesarean section and infant intensive care unit admission[21].

Overt hypothyroidism and child neurodevelopmental outcomes.—Thyroid hormone affects neuronal migration, connection, myelination and synaptogenesis and is thus essential for normal brain development[22,23]. Thyroid hormone receptors are expressed during cortex development[24,25]. The adverse effects of maternal thyroid hypofunction in child neurodevelopment were first reported in a series of studies in the 1970s[26,27]. In a subsequent seminal study published in 1999, 62 children born to hypothyroid women (median TSH 13.2 mIU/l) had an average IQ that was four points lower at 7–9 years of age than that of 124 children born to euthyroid women (median TSH 1.4 mIU/l)[28].

Furthermore, when 14 women with hypothyroidism who were treated with levothyroxine during pregnancy were excluded from the analysis, the difference in IQ was seven points.

Subclinical hypothyroidism, hypothyroxinaemia and obstetric outcomes.—The effects of maternal subclinical hypothyroidism and isolated hypothyroxinaemia (that is, low serum levels of free T_4 with normal levels of TSH) on obstetric outcomes have been debated. For example, several observational studies have found no associations between maternal subclinical hypothyroidism and outcomes including miscarriage, gestational diabetes mellitus, gestational hypertension, pre-eclampsia, preterm labour, premature delivery, low birthweight and high birthweight[29–31]. Furthermore, a meta-analysis and systematic review of ten cohort studies including 48,684 women (which included some of the observational studies discussed in the previous sentence) similarly showed no significant associations between maternal subclinical hypothyroidism or isolated hypothyroxinaemia and preterm birth[32].

On the other hand, multiple other observational cohort studies have found associations between maternal subclinical hypothyroidism and pregnancy loss or miscarriage[33,34], prematurity or preterm birth[35,36], placental abruption[35] and neonatal intensive care unit admission and respiratory distress syndrome in infants[35]. A meta-analysis of 18 cohort studies including almost 4,000 women found that compared with euthyroidism, maternal subclinical hyperthyroidism is associated with increased risks of pregnancy loss (relative risk (RR) 2.01, 95% CI 1.66–2.44), placental abruption (RR 2.14, 95% CI 1.23–3.70), premature rupture of membranes (RR 1.43, 95% CI 1.04–1.95) and neonatal death (RR 2.58, 95% CI 1.41–4.73)[37]. In a 2020 retrospective study in 8,413 pregnant women, offspring of women with subclinical hypothyroidism had increased risks of prematurity (RR 2.15, 95% CI 1.14–4.03) and neonatal respiratory distress syndrome (RR 2.8, 95% CI 1.01–7.78) compared with the risks in euthyroid women. Furthermore, the risks of these adverse outcomes were even higher if subclinical hypothyroidism was present in the first trimester[38]. In addition, an individual-participant level meta-analysis of data published in 2019 from 19 cohort studies (including 47,045 pregnant women) similarly showed increased risks of preterm birth in women with subclinical hypothyroidism (OR 2.9, 95% Cl 1.01–1.64) and isolated hypothyroxinaemia (OR 1.46, 95% Cl 1.12–1.90)[39].

These conflicting results regarding the effects of maternal subclinical hypothyroidism across cohort studies might be due to variability in timing of TSH measurements, differences in TSH cut-off values used for the diagnosis of subclinical hypothyroidism, and variability in assessment of thyroid peroxidase (TPO) antibody status. However, evidence is mounting that maternal subclinical hypothyroidism is associated with miscarriage and preterm birth. The effects of isolated maternal hypothyroxinaemia on pregnancy outcomes remain unclear[40].

Subclinical hypothyroidism, hypothyroxinaemia and child neurodevelopmental outcomes.—Mild maternal thyroid hypofunction has been shown to have a deleterious effect on child neurodevelopmental outcomes in multiple cohorts. In a study of 3,839 Dutch mother–child pairs, both low and high maternal levels of free T_4 in early pregnancy were associated with lower child IQ and higher likelihood of an IQ of <85 at 6–8 years of age compared with normal levels of maternal free T_4 (REF.[41]).

This association remained statistically significant even when overt hypothyroidism and overt hyperthyroidism were excluded. Of note, in this analysis, maternal serum TSH values did not predict child IQ. Brain MRI has shown alterations in child neuroanatomy associated with either low or high maternal thyroid function; the strongest effect was observed when thyroid function was measured at 8–14 weeks gestation. These findings suggest that 8–14 weeks gestation is a critical period for the effects of thyroid hormone on fetal brain development[42]. Of note, a longitudinal study in 4,615 UK mother–child pairs did not show significant associations between maternal levels of TSH or free T_4 levels measured in the first trimester and the standardized test scores of children from the age of 54 months through to 15 years[43]. However, a 2018 meta-analysis of 26 studies found significant associations between maternal subclinical hypothyroidism or hypothyroxinaemia and measures of child intellectual disability such as low IQ, language delay or global developmental delay (OR 2.14, 95% CI 1.2–3.83, for subclinical hypothyroidism and OR 1.63, 95% CI 1.03–2.56, for hypothyroxinaemia, both compared with children of euthyroid women)[44]. Although questions remain to be answered, observational data strongly suggest an association between maternal levels of free T_4 in early pregnancy and child developmental outcomes.

Levothyroxine treatment for subclinical hypothyroidism and hypothyroxinaemia.—Only a few randomized controlled trials (RCTs) have assessed the benefit of levothyroxine treatment for maternal subclinical hypothyroidism and/or hypothyroxinaemia[45]. A RCT of 366 TPO antibody-negative pregnant Iranian women with TSH 2.5–10 mIU/l assessed the effects of levothyroxine treatment versus no therapy (randomization at 11–12 weeks gestation) on preterm birth[46]. Overall, no difference was observed in the prevalence of preterm delivery between treated and untreated women. However, in a sensitivity analysis in which the sample was restricted to women with a baseline TSH of 4–10 mIU/l, levothyroxine treatment did decrease preterm delivery risk (7.3% versus 19%, $P = 0.04$). A 2019 meta-analysis of seven cohort studies and six RCTs (including women undergoing assisted reproductive technology) showed a 17% decrease in risk of pregnancy loss in women with subclinical hypothyroidism who received levothyroxine treatment (95% CI 0.72–0.97), although heterogeneity was noted in the timing of intervention and the TSH cut-off values used[47].

A pair of RCTs in the USA randomized 677 pregnant women with subclinical hypothyroidism (defined as TSH ≥4 mIU/l with normal free T_4) and 526 women with hypothyroxinaemia (defined as free T_4 <0.86 ng/dl) to either levothyroxine or placebo treatment at a median gestational age of 16.7 weeks[48]. No significant differences were noted in child neurodevelopmental scores at up to 60 months of age between children of the levothyroxine-treated women and the placebo-treated women. In addition, levothyroxine treatment for subclinical hypothyroidism or hypothyroxinaemia did not alter pregnancy outcomes, including preterm birth, gestational hypertension, pre-eclampsia, gestational diabetes mellitus, stillbirth or miscarriage, low birthweight or respiratory distress syndrome. In this study, levels of TSH were monitored throughout pregnancy and the levothyroxine doses in the treatment groups were adjusted for a goal TSH of 0.1–2.5 mIU/l. In another RCT, the Controlled Antenatal Thyroid Screening Study (CATS), 390 pregnant women with subclinical hypothyroidism or hypothyroxinaemia who were treated with 150 μg daily

levothyroxine were compared with 404 untreated pregnant women[49]. Treatment did not result in significant differences in mean child IQ or the proportion of children with an IQ of <85 at 3 years of age. A follow-up study of these children at 9 years of age again showed no difference in IQ between children of treated and children of untreated mothers[50]. Of note, the levothyroxine dose employed in this study was high, potentially resulting in over-treatment, although a secondary analysis including only those with high free T_4 had similar results. A major limitation of both of these trials is that the intervention was initiated well into the second trimester (median gestational age at randomization was 16.7 weeks in the US study[48] and 12.3 weeks in CATS)[49,50]. As the fetus depends entirely on maternal thyroid hormone during the first trimester, both trials may have missed the critical window for assessing the potential benefits of maternal levothyroxine supplementation.

Overall, limited data from RCTs suggest that levothyroxine treatment in pregnant women with subclinical hypothyroidism, especially those with TSH >4 mIU/l, might decrease risks of preterm delivery and pregnancy loss when initiated in early pregnancy. Levothyroxine treatment has not shown any notable benefit for child neurodevelopmental outcomes, but trials have been limited by initiation of therapy fairly late in gestation. Additional RCTs are needed to determine the effect of levothyroxine treatment on adverse obstetric and child neurodevelopment outcomes, when treatment is initiated in the first trimester.

Thyroid autoimmunity.—Thyroid autoimmunity can occur in the presence or absence of thyroid dysfunction. In regions with adequate iodine nutrition, autoimmune thyroiditis (Hashimoto thyroiditis) is the most common cause of hypothyroidism. TPO and thyroglobulin antibodies are frequently elevated in autoimmune thyroiditis. The prevalence of TPO and thyroglobulin antibody positivity (indicators of thyroid autoimmunity) in pregnant women is estimated to be 5–14% and 3–18%, respectively[51]. Underlying thyroid autoimmunity seems to have an additive or synergistic effect on miscarriage[34] and prematurity[36] risk, when combined with maternal subclinical hypothyroidism. Thyroid autoimmunity itself might also have adverse effects in pregnancy, even in the absence of thyroid dysfunction. Meta-analyses of pregnancy in euthyroid women have shown a twofold to fourfold increase in the risk of recurrent miscarriage associated with thyroid autoimmunity[52,53]. Similarly, euthyroid pregnant women with TPO antibody positivity have been shown to have twofold to threefold increased risks of preterm birth[34,39,52]. The adverse effects of TPO antibody positivity might be due, at least in part, to increased risk of hypothyroidism as pregnancy progresses[54]. In a Dutch cohort study, TPO antibody-positive women had a higher risk of premature delivery than TPO antibody-negative women; however, this effect was negated if the TPO antibody-positive women showed an appropriate increase in thyroid hormone synthesis in response to hCG[55]. Of note, TPO antibody positivity could potentially just be a marker for other forms of autoimmunity and the observed increased rates of pregnancy loss in TPO antibody-positive women could be mediated by the presence of non-organ-specific autoantibodies rather than by thyroid status[51].

A few RCTs have assessed the benefits of levothyroxine treatment in euthyroid TPO antibody-positive pregnant women. A RCT of 393 euthyroid pregnant Italian women with positive TPO antibody titres found no significant differences in the rates of miscarriage

and preterm delivery between levothyroxine-treated and untreated women. However, 49% of women randomized to the no-treatment group were then treated with levothyroxine owing to a serum level of TSH of >3 mIU/l occurring in the second or third trimester[56]. Both the TPO antibody-positive levothyroxine-treated and untreated groups had higher rates of miscarriage and preterm delivery than the TPO antibody-negative euthyroid women. Another RCT in 131 TPO antibody-positive women showed a decrease in preterm delivery risk in levothyroxine-treated women compared with untreated women (RR 0.3, 95% CI 0.1–0.85), but only in those with a baseline serum TSH of >4 mIU/l[57].

Other studies have explored the impact of levothyroxine treatment initiated before conception. The Pregnancy Outcomes Study in Euthyroid Women with Thyroid Autoimmunity after Levothyroxine trial assessed the benefit of levothyroxine treatment in 565 Chinese TPO-positive euthyroid women who were undergoing in vitro fertilization[58]. Levothyroxine treatment, initiated before conception and continued through delivery, did not have a significant effect on rates of miscarriage or live birth. Similarly, the Thyroid Antibodies and Levothyroxine trial in 952 euthyroid UK women with positive TPO antibody titres and a history of miscarriage or infertility showed no differences in the rates of live births, pregnancy loss, preterm birth or neonatal outcomes when levothyroxine was initiated before conception[59]. A 2021 systematic review and meta-analysis of six RCTs assessing the effect of levothyroxine treatment in euthyroid women with thyroid autoimmunity did not find any statistically significant differences in the relative risks of pregnancy achieved, miscarriage, preterm delivery or live birth[60].

Current recommendations for screening for hypothyroidism in pregnancy.— There is general agreement that any pregnant woman with symptoms and signs suggestive of overt hypothyroidism should have her thyroid function evaluated, although many symptoms might overlap the normal effects of pregnancy. The presence of underlying risk factors for thyroid dysfunction (BOX 1) could be helpful in determining who should be tested. However, universal screening for thyroid dysfunction in asymptomatic pregnant women is controversial. Such universal screening strategies would detect overt hypothyroidism, for which there is a dear treatment benefit, in about 0.5% of pregnant women. However, universal screening would also uncover far more cases of subclinical hypothyroidism, in about 3.5% of pregnant women, for which the benefits of treatment remain uncertain[2]. Therefore, there is currently no consensus regarding routine screening for thyroid dysfunction in pregnant women.

The ATA and European Thyroid Association (ETA) both state that insufficient evidence exists to recommend for or against universal TSH screening at the first trimester antenatal visit[6,61]. By contrast, ACOG and the American Society of Reproductive Medicine recommend against universal screening for thyroid disease in pregnant women[13,62]. Of note, the ATA does recommend aggressive case-finding strategies to identify pregnant women who are at increased risk for thyroid hypofunction (BOX 1). A retrospective single-centre study has suggested that these case-finding criteria identify fewer pregnant women with subclinical hypothyroidism but a comparable proportion with overt hypothyroidism, compared with a universal screening strategy[63]. On the other hand, several observational studies and a meta-analysis have suggested that such a case-finding approach, even based on

the recommended criteria by the ATA, might miss up to 40–50% of pregnant women with thyroid dysfunction in whom treatment would be recommended[64–66].

Recommendations for treatment of hypothyroidism in pregnancy.—Overt hypothyroidism should be treated to prevent adverse effects on pregnancy and child developmental outcomes[6,13]. Regarding maternal subclinical hypothyroidism, the 2017 ATA guidelines recommend utilizing TPO antibody status along with serum levels of TSH to guide treatment decisions (TABLE 1). Neither ATA nor ACOG currently recommends levothyroxine treatment for isolated hypothyroxinaemia[6,13]. However, ATA and ACOG do have differences in their recommendations due to differing interpretations of currently available evidence. For example, ACOG does not recommend treatment of subclinical hypothyroidism in pregnancy due to the lack of clear benefit of levothyroxine treatment for child neurodevelopmental outcomes. By contrast, the ATA recommends treatment of subclinical hypothyroidism with levothyroxine, especially in the presence of thyroid autoimmunity. This recommendation is based on the mounting observational evidence regarding increased risk of adverse obstetric outcomes in pregnant women with subclinical hypothyroidism, and data from small trials suggesting a treatment benefit. Given the currently available evidence, and the safety and ease of levothyroxine treatment, the authors agree with the treatment of pregnant women with serum concentrations of TSH that are greater than pregnancy-specific reference ranges or >4 mIU/l, regardless of TPO antibody status.

During pregnancy, levothyroxine monotherapy should be used for thyroid hormone replacement[6,13]. The use of liothyronine, levothyroxine–liothyronine combination therapy, or desiccated thyroid is not recommended in pregnancy, as liothyronine does not cross the blood–brain barrier to the fetal brain[67]. Consequently, liothyronine-containing treatment options might normalize maternal serum levels of TSH but result in inadequate thyroid hormone availability for the fetus. Once levothyroxine therapy is started in a pregnant woman, serum levels of TSH should be measured every 4–6 weeks until mid-gestation, then once in the second and third trimesters for a goal serum level of TSH of <2.5 mIU/l[6,13]. Most women who are on levothyroxine before conception will require a 25–30% increase in their levothyroxine dose once pregnant, in order to maintain euthyroidism in the setting of the oestrogen-induced increase in serum levels of TBG[68,69]. Levothyroxine can be decreased back to the pre-pregnancy dose after delivery.

Hyperthyroidism in pregnancy

Aetiology of hyperthyroidism in pregnancy.—Graves disease and gestational transient thyrotoxicosis (GTT) are the two most common causes of hyperthyroidism in pregnancy. The prevalence of new-onset Graves disease in pregnant women is estimated to be 0.05%[70], whereas that of GTT ranges from 2% to 11%[71,72]. As the body's autoimmune response generally decreases as pregnancy progresses, the incidence of Graves hyperthyroidism decreases in the second and third trimesters after a slight increase in the first trimester[73,74]. Distinguishing between the two forms of hyperthyroidism seen in pregnancy is important, as the disease course and treatment options differ. GTT is mediated by high serum levels of hCG occurring in early pregnancy. As high levels of hCG are

also associated with hyperemesis[75,76], GTT is usually associated with symptoms of nausea and/or vomiting. In both GTT and Graves disease, laboratory testing will demonstrate suppressed serum levels of TSH and elevated levels of thyroid hormone. Patients with Graves disease often have an increased ratio of T_3 to T_4 (≥20:1), as preferential production of T_3 occurs in Graves disease. By contrast, serum levels of T_3 are often lower in women with GTT in the setting of hyperemesis.

Of note, antibodies specific for the thyrotropin receptor (TRAb) are generally detectable in Graves disease but are absent in GTT[70]. TRAb can be assessed as TSH receptor-binding immunoglobulin, which measures both stimulating and blocking antibodies without distinction. Alternatively, thyroid-stimulating immunoglobulin can be measured, which specifically measures stimulating TRAb[77]. Women with Graves disease typically report thyrotoxic symptoms, such as unintentional weight loss, palpitations, hand tremors and heat intolerance, which might have been present prior to pregnancy. By contrast, patients with GTT rarely have severe thyrotoxic symptoms and they lack typical signs of Graves disease such as diffuse goitre and Graves ophthalmopathy. GTT spontaneously resolves as hCG levels decrease after about 10–12 weeks gestation and the condition is not associated with adverse pregnancy outcomes[78,79]. Therefore, patients with GTT can be treated with supportive measures for nausea, vomiting and any electrolyte imbalance or volume depletion if they have concurrent hyperemesis gravidarum, but these patients do not require antithyroid drug therapy.

Effects of hyperthyroidism on pregnancy outcomes.—Other than GTT, untreated overt hyperthyroidism in pregnancy is associated with maternal and fetal complications including pre-eclampsia, pregnancy loss, maternal and fetal congestive heart failure, maternal thyroid storm, preterm labour, intrauterine growth retardation, low birthweight, and fetal and/or neonatal hyperthyroidism[19,21,80,81]. However, subclinical hyperthyroidism is not associated with such adverse obstetric outcomes[82].

Treatment options for Graves hyperthyroidism in pregnancy.—If treatment of overt hyperthyroidism is indicated, antithyroid drugs or thyroidectomy can be considered in pregnancy. Radioactive iodine ablation is contraindicated during gestation given its teratogenic effects[6]. Methimazole and propylthiouracil are antithyroid drugs available in the USA and Europe. In Europe, carbimazole (a drug that is rapidly metabolized to methimazole after ingestion) is also available. All antithyroid drugs are equally effective in treating Graves disease, but their adverse effects differ. Methimazole, carbimazole and propylthiouracil can increase serum levels of liver enzymes, which generally normalize after improvement of thyrotoxicosis[83] or discontinuation of medication[84]. A meta-analysis of 15 studies including both non-pregnant adults and pregnant women showed increased odds of elevated levels of liver enzymes associated with propylthiouracil compared with methimazole (OR 2.4, 95% CI 1.16–4.96)[85]. Propylthiouracil has also been associated with rare but potentially fatal fulminant hepatic failure, including in pregnant women[86,87]. Thus, methimazole or carbimazole is generally preferred over propylthiouracil in non-pregnant patients.

The risk of teratogenicity must be considered when choosing antithyroid drugs in pregnancy and the preconception period. Previously, only methimazole or carbimazole, but not propylthiouracil, was thought to cause birth defects. However, studies from the past decade have shown that methimazole, carbimazole and propylthiouracil are all teratogenic[88–92]. A Danish registry study found that 8–9% of children exposed to these antithyroid drugs in utero had birth defects compared with about 5–6% of non-exposed children[92]. Similarly, a large Korean study found a 7.2% risk of birth defects with antithyroid drug exposure in the first trimester compared with 5.9% without antithyroid drug exposure[91]. Compared with children of non-exposed women (whose rate of birth defects was 5.94 cases per 1,000 live births), the absolute risk of birth defects was higher in children of women exposed to antithyroid drugs during pregnancy: 8.81, 17.05 and 16.53 cases per 1,000 live births following exposure during the first trimester to propylthiouracil alone, methimazole alone and both propylthiouracil and methimazole, respectively[91]. A 2020 meta-analysis of seven studies of first-trimester pregnant women also showed a higher risk of birth defects in women exposed to methimazole or carbimazole compared with propylthiouracil (OR 1.29, 95% CI 1.09–1.53)[85]. Methimazole or carbimazole exposure is associated with more severe birth defects, including aplasia cutis, oesophageal or choanal atresia, and ventricular septal defects, whereas propylthiouracil exposure is associated with less severe defects including cystic malformations of the face or neck, hydronephrosis, and cysts in the urinary tract[88]. Given these findings, propylthiouracil is the preferred antithyroid drug in the first trimester. If a pregnant woman continues to require antithyroid drugs beyond 16 weeks gestation, it is unclear whether the antithyroid drug should be changed to methimazole, given concern for suboptimal control of hyperthyroidism during dose titration of the new antithyroid drug. If needed, a propylthiouracil to methimazole dose ratio of 20 to 1 can be used to switch[6].

In pregnant women with severe hyperthyroidism who cannot tolerate antithyroid drugs, or when hyperthyroidism is not adequately controlled with medical treatment, thyroidectomy can be considered. The second trimester is the safest for thyroidectomy, given the potential risk of teratogenicity from anaesthesia in the first trimester and increased risk of preterm delivery in the third trimester[6].

Adequate thyroid hormone is critical for normal fetal development, especially in early pregnancy. Antithyroid drugs cross the placenta and can affect fetal thyroid hormone production once the fetal thyroid becomes functional at mid-gestation. Therefore, it is important to avoid over-treatment of hyperthyroidism in pregnancy. A Japanese study demonstrated that antithyroid drugs might cause fetal hypothyroidism even when maternal thyroid function is normal[93]. Thus, the ATA recommends targeting a maternal level of free T_4 that is high-normal to mildly elevated when treating hyperthyroidism in pregnancy. Furthermore, thyroid function should be monitored every 2–4 weeks until a pregnant woman is on a stable dose of antithyroid drugs, then every 4 weeks thereafter[6]. Of note, thyroid autoimmunity might improve in the second trimester due to pregnancy-induced immune tolerance, therefore pregnant women might require decreasing doses of antithyroid drugs. The ‘block-and-replace’ strategy, using both antithyroid drugs and levothyroxine, is not recommended in pregnancy, as antithyroid drugs cross the placenta to a much greater extent than levothyroxine and this strategy can lead to fetal hypothyroidism.

TRAb can cross the placenta and cause fetal hyperthyroidism and goitre when present in high levels. Furthermore, TRAb titres can remain elevated for years after thyroidectomy or radioactive iodine ablation of the thyroid gland. Therefore, all pregnant women with active Graves hyperthyroidism or a history of ablative treatment for Graves disease should have serum TRAb titres measured in the first trimester. If the TRAb titre is more than 3 times the upper limit of the reference range, the measurement should be made again at 18–22 weeks gestation when the fetal thyroid gland fully matures. When the TRAb titre remains elevated above 3 times the upper limit of the reference range by mid-gestation, consultation with maternal-fetal medicine and neonatology is warranted to monitor for fetal and neonatal hyperthyroidism and goitre.

Preconception counselling and treatment options for women with Graves disease.—Women of reproductive age who are diagnosed with Graves disease should be counselled regarding plans for pregnancy, given the potential adverse effects of both antithyroid drugs and uncontrolled overt hyperthyroidism in pregnancy. Pregnancy should be postponed until women are euthyroid. Propylthiouracil might be preferred over methimazole in the preconception setting to avoid methimazole exposure during the period of organogenesis in early pregnancy[6]. In some women, antithyroid drugs can be discontinued as soon as pregnancy is confirmed, with close thyroid function monitoring undertaken, in the hope that hyperthyroidism will not recur until the second trimester when the potential teratogenic effects of antithyroid drugs are no longer a concern. This strategy is appropriate only in carefully selected women who require a low dose of antithyroid drugs to maintain euthyroidism (up to 5–10 mg of methimazole a day or 100–200 mg of propylthiouracil a day), have been treated with antithyroid drugs for at least 6 months, do not have Graves ophthalmopathy and have a low or negative TRAb titre[6].

If women prefer to avoid antithyroid drug use during pregnancy, definitive therapy with thyroidectomy or radioactive iodine ablation can be considered before conception. Serum levels of TRAb generally decrease within a year after thyroidectomy, but can transiently increase and remain elevated for years after radioactive iodine treatment[94]. After definitive treatment, it is prudent to avoid conception until women are euthyroid on a stable dose of levothyroxine. Pregnancy should be avoided for 6 months after radioactive iodine treatment[95].

Iodine nutrition in pregnancy

Iodine requirements in pregnancy

Iodine is an essential micronutrient that is required for thyroid hormone production. Iodine requirements increase in pregnancy due to several factors. First, increased demand occurs for maternal thyroid hormone production owing to the thyrotrophic effects of hCG and oestrogen-mediated increases in TBG. Second, iodine is transferred to the fetus, especially after the fetal thyroid gland matures at 18–20 weeks gestation. Third, increases in renal clearance of iodine occur, owing to increased blood volume and glomerular filtration in pregnancy[96] (FIG. 1). Thus, increased iodine intake from 150 μg per day in non-pregnant adults to 220–250 μg per day during pregnancy is recommended[97,98] (TABLE 2).

Spot urinary iodine concentrations (UIC) can be used to assess iodine status at the population level[99,100]. A median UIC of 150–249 μg/l is consistent with adequate iodine status[99] (TABLE 3). Currently, no biomarker exists for chronic iodine nutritional status at the individual level, as UIC only reflects recent (past 6–8 h) iodine intake[101].

Epidemiology of iodine deficiency

Given the increased iodine requirements in gestation, pregnant women might be at risk of iodine deficiency even when the general population is iodine-sufficient[102]. Only one-third of the 31 European countries with available data report adequate iodine intake in pregnancy[103]. In addition, pregnant women in the USA. are currently considered mildly iodine-deficient, with a median UIC of 144 μg/l in assessments performed during 2007–2014 (REFS[104,105]). A fourfold increase was noted in the proportion of US women of childbearing age with UIC <50 μg/l in assessments performed during 2005–2010 compared with prior years[104,106,107].

Severe iodine deficiency in pregnancy

Severe iodine deficiency in pregnancy can cause maternal hypothyroidism. Severe iodine deficiency has been associated with increased risks of miscarriage, premature birth and stillbirth[108,109]. Chronically low iodine intakes of <50 μg per day might also lead to maternal and fetal goitre[110,111]. Iodine intakes of <25 μg per day in pregnancy could lead to children being born with cretinism, characterized by severe intellectual disability, deaf-mutism and stunted growth[112,113]. Meta-analyses have shown that children born to women with severe iodine deficiency have an IQ lower by 7.4 to 12 points compared with children born to iodine-sufficient women[114,115].

Mild-moderate iodine deficiency in pregnancy

Many observational studies have found associations between mild-to-moderate iodine deficiency in pregnancy and risk of miscarriage[116], preterm birth[117–119], pre-eclampsia[118], low birthweight[117,118], and neonatal intensive care unit admission[119]. However, these findings have not been universal[120]. The effects of maternal mild-to-moderate iodine deficiency on child neurodevelopment are unclear. Observational studies have shown lower verbal IQ and reading skills at 8 years of age[121] and lower language skills assessment score at 9 years of age[122] in children born to mothers with UIC <150 μg/g creatinine or 150 μg/l compared with children born to mothers with higher UIC levels. Other studies have shown that children born to mothers with maternal mild-to-moderate iodine deficiency show poorer working memory at 4 years of age[123], lower scores in psychomotor development assessment at 12 months of age[124], lower verbal IQ at 6–12 years of age[125], and lower cognitive, language and motor scores in children at 18 months of age[126], compared with those born to iodine-sufficient mothers. A 2019 meta-analysis of individual data from three population-based cohorts including 6,180 mother-child pairs also showed associations between maternal UIC <150 μg/g creatinine or ≥500 μg/g creatinine with decreased verbal IQ scores assessed at 1.5–8 years of age[127]. However, other observational studies have failed to show notable associations between maternal iodine deficiency and child IQ[127,128]. The few available RCTs assessing iodine supplementation for women with mild-to-moderate iodine deficiency in pregnancy have not shown a clear benefit for child neurodevelopmental outcomes. Of note, these studies have been limited by non-randomized or inadequately

powered designs, initiation of supplements too late in pregnancy or by being conducted in areas of only borderline iodine deficiency[129,130].

Current recommendations for iodine intake

Universal salt iodization is considered the most effective way to improve iodine status at the population level[131]. However, salt iodization has not been mandated in many countries including the USA and much of Europe. Therefore, many societies, including the ATA[6], the Endocrine Society[132], the US Teratology Society[133], the American Academy of Pediatrics[134] and the ETA[61], currently recommend that women who are planning to be pregnant, are pregnant or are breastfeeding should take a daily oral supplement containing 150 μg of iodine.

Thyroid nodules and cancer in pregnancy

Thyroid nodules in pregnancy

The estimated prevalence of thyroid nodules in pregnant women ranges from 3% to 29%, depending on iodine intake[6,7]. Older age, increased number of previous pregnancies, and low or excessive iodine nutritional status are associated with an increased risk of thyroid nodules in pregnancy[135,136]. A prospective cohort study of 221 pregnant Chinese women found a 15% prevalence of thyroid nodules ≥2 mm in the first trimester, with a median increase of 5 mm in nodule size occurring during pregnancy[135]. Nodule size might increase during gestation due to the thyrotrophic effects of hCG and due to TSH stimulation resulting from depletion of iodine stores[137,138]. In addition to the structural similarity between hCG and TSH, structural similarities also exist between hCG and TSH receptors[5]. Consequently, high serum levels of hCG can potentially stimulate TSH receptors on the thyroid gland; this effect can lead to the development of thyroid nodules or gland hyperplasia, in addition to increased thyroid hormone production.

Thyroid ultrasonography is the best imaging modality for the evaluation of thyroid nodules found in pregnant women. This modality can also be used for patient risk stratification using the same characteristics as in non-pregnant adults. Using pregnancy-specific reference ranges, serum levels of TSH should be checked in pregnant women with thyroid nodules to screen for hyperfunctioning nodules, which are unlikely to be malignant. Of note, nuclear thyroid scans using radioactive iodine tracer are contraindicated in pregnancy. In pregnant women with thyroid nodules, a serum level of TSH that remains suppressed beyond 16 weeks gestation suggests the presence of a toxic adenoma (that is, a single hyperfunctioning thyroid nodule) and fine needle aspiration (FNA) biopsy can be delayed until nuclear scanning is feasible after delivery. If toxic adenoma is unlikely and the nodule meets criteria for cytological evaluation, FNA biopsy of thyroid nodule(s) can be safely performed in pregnancy[138]. Nodules that are cytologically benign can be managed in the same way as in non-pregnant adults. If cytology shows indeterminate results, including atypia of unknown significance or follicular lesion of unknown significance, FNA biopsy can be repeated for further evaluation. Molecular testing is not currently recommended in pregnancy, as it is not yet clear how pregnancy affects the results of molecular markers[138]. For indeterminate

nodules without characteristics suggestive of an aggressive cancer, repeat FNA biopsy can be deferred until after pregnancy.

Thyroid cancer in pregnancy and postpartum

Although the prevalence of thyroid cancer in pregnant women is difficult to estimate, the incidence of thyroid cancer in young adults has been increasing in the last two to three decades, especially in young women of reproductive age[8–10]. A large retrospective study using the 1991–1999 California Cancer Registry showed that thyroid cancer was the second most common cancer in the perinatal period among all cancers recorded in the registry, with a prevalence of 14.4%. This study showed 3.3 occurrences of thyroid cancer per 100,000 cancer cases found within 9 months before pregnancy, 3 occurrences of thyroid cancer per 100,000 cancer cases found at delivery, and 10.8 occurrences of thyroid cancer per 100,000 cancer cases found within 1 year of delivery[139]. An assessment of 595 women diagnosed with thyroid cancer between 9 months before to 12 months after delivery from the same cohort in 1991–1995 did not show any statistically significant differences in maternal or neonatal outcomes compared with pregnant women without thyroid cancer[140]. In addition, no difference was observed in survival between women with thyroid cancer diagnosed in the perinatal period and non-pregnant women with thyroid cancer.

Given the overall good prognosis of differentiated thyroid cancer (DTC) in young women and the potential anxiety associated with a new cancer diagnosis[141], FNA biopsy of many thyroid nodules can be deferred until after pregnancy, if the patient prefers. Small studies have shown that delaying diagnosis and treatment of thyroid cancer until after pregnancy does not result in worse outcomes. For example, no differences were observed in long-term survival[142], changes in tumour volume[143,144] or development of lymph node metastases[143,144] between those who were treated during pregnancy and those who deferred treatment. Therefore, the ATA recommends that most pregnant women with newly diagnosed DTC can be monitored conservatively with serial thyroid ultrasonography during pregnancy. If evidence is found of notable tumour growth by mid-gestation or development of metastatic disease, thyroid surgery can be considered. When required, thyroidectomy is safest in the second trimester[138]. No evidence is available to support the use of suppressive therapy with levothyroxine when thyroid cancer surgery is deferred.

In a small study, stimulation of TSH and oestrogen receptors by hCG in pregnancy has been implicated in increased tumour aggressiveness in DTC[145]. Two Italian studies found an increased risk of persistent or recurrent disease in patients when DTC is diagnosed during pregnancy[145,146]. However, both of these studies defined recurrent or persistent disease based on serum levels of thyroglobulin only, without evaluation for structural disease. Furthermore, neither study showed an increased risk of recurrent or persistent disease when surgery was delayed until after pregnancy. In light of current evidence regarding long-term outcomes in patients with DTC diagnosed in pregnancy, we agree with the current recommendation by the ATA for diagnosis and treatment of DTC diagnosed in pregnancy as described above.

Studies assessing the potential effects of pregnancy on anaplastic or medullary thyroid cancer are lacking. However, thyroid surgery in pregnancy should be strongly considered given the aggressive nature of these cancers.

If radioactive iodine ablation is indicated as an adjunctive treatment for thyroid cancer, it should be delayed until after delivery. Iodine is taken up into the lactating mammary gland via the sodium iodide symporter[147]. As such, women should be counselled to stop breastfeeding at least 6 weeks to 3 months prior to I^{131} radioactive iodine treatment in order to prevent potential adverse effects of radiation on breast tissues and breastfed infants[95].

Those with a history of thyroid cancer

Having a history of thyroid cancer should not deter patients from pursuing pregnancy. A large Korean study utilizing national insurance data from 2006–2014 showed no statistically significant increase in adverse pregnancy outcomes including caesarean section, preterm birth, pre-eclampsia, placental abruption, placental previa, stillbirth, low birthweight and large for gestational age, in women with a history of thyroid cancer[148]. In a study of 235 pregnant women in the USA with a history of DTC, disease recurrence and progression were monitored using imaging (ultrasonography, CT scan or radioactive iodine scans), serum levels of thyroglobulin and thyroglobulin antibody, and clinical evaluation within 12 months before and after pregnancy[149]. Women who had an excellent, indeterminate or biochemical incomplete response to treatment per the 2015 ATA guidelines[138] prior to pregnancy had no evidence of structural recurrence or progression of thyroid cancer on evaluation at 3–12 months after delivery, although a small number of women had an increase in serum levels of thyroglobulin and thyroglobulin antibody. By contrast, 29% of women who had a structural incomplete response to therapy prior to pregnancy had tumour progression, defined as a ≥3 mm increase in the size of pre-existing disease or identification of a new metastasis, at postpartum evaluation. Therefore, women with a response to therapy classified as excellent or indeterminate according to ATA guidelines prior to pregnancy do not require increased surveillance, but those with an incomplete response before pregnancy should be closely monitored during gestation. As subclinical hyperthyroidism is not associated with adverse obstetric outcomes[82], serum TSH goals for cancer survivors are the same in pregnant women as in non-pregnant adults[138]. Most women will require an increase in their levothyroxine dose by 25–30% during pregnancy to maintain TSH targets, due to increased TBG levels.

Postpartum thyroiditis

Epidemiology

Postpartum thyroiditis is a destructive thyroiditis that occurs in 5–8% of women within the first 12 months after delivery[150]. The aetiology is thought to be a rebound of underlying thyroid autoimmunity occurring after the immune tolerance induced by pregnancy has ended. This mechanism is proposed because postpartum thyroiditis is more commonly seen in women who are positive for TPO antibodies[151] or those with a personal or family history of autoimmune diseases[152]. Postpartum thyroiditis can also occur after miscarriage or pregnancy loss, as well as in women on levothyroxine replacement for underlying Hashimoto thyroiditis[153].

Disease course

Postpartum thyroiditis classically presents as thyrotoxicosis within 4–8 weeks of delivery, due to release of preformed thyroid hormones from an inflamed thyroid gland. This thyrotoxic phase typically lasts for 1–2 months and can be followed by transient hypothyroidism lasting 4–6 months until the thyroid gland recovers (FIG. 2). However, the disease course can vary; ~25% of women only have a thyrotoxic phase and 50% of women only have a hypothyroid phase[150]. The majority of women recover completely and return to a euthyroid state within a year, but up to 50% will develop persistent hypothyroidism even after initial recovery[154,155]. Women who are positive for serum TPO antibodies are at increased risk of developing permanent hypothyroidism after postpartum thyroiditis[155]. Postpartum thyroiditis recurs after up to 70% of subsequent pregnancies[150].

Evaluation and treatment

Distinguishing the thyrotoxic phase of postpartum thyroiditis from new or recurrent Graves disease is important, as treatment options differ. Antibody testing for TRAb is helpful, as it is a highly specific and sensitive biomarker for Graves disease. By contrast, serum levels of TPO antibody can be elevated in both postpartum thyroiditis and Graves hyperthyroidism[156]. The ratio of T_3 to T_4 is often higher (>20:1) in Graves disease due to preferential T_3 production[157]. Graves disease most frequently presents at 6–12 months after delivery, compared with a presentation at 1–4 months after delivery for postpartum thyroiditis[152]. Of note, I^{123} radioactive iodine uptake and scan can be employed to differentiate postpartum thyroiditis from Graves disease if needed. Iodine uptake is low in the thyrotoxic phase of postpartum thyroiditis, whereas it is elevated in Graves disease. However, TRAb measurement is usually adequate to differentiate between the two entities.

As the thyrotoxic phase of postpartum thyroiditis is transient and results from the release of preformed hormones, rather than increased thyroid hormone synthesis, antithyroid drugs are not useful. Notable thyrotoxic symptoms, such as palpitations or anxiety, can be managed with β-adrenergic agonists that are safe for use during lactation (for example, metoprolol or propranolol). Levothyroxine can be employed for the hypothyroid phase if women are symptomatic or are actively trying to conceive. Around 6–12 months after diagnosis, levothyroxine treatment can be tapered as hypothyroidism is usually transient. However, given the increased risk of recurrent hypothyroidism in women who recover from postpartum thyroiditis, these women should have yearly monitoring of TSH and should be monitored for recurrent postpartum thyroiditis after subsequent pregnancies. Selenium supplementation has been explored for its possible anti-inflammatory effect in autoimmune thyroiditis[51]. However, trials of selenium supplementation in pregnancy have shown mixed results[158]. Thus, selenium supplementation for prevention or treatment of postpartum thyroiditis is currently not recommended[6].

Conclusions

Thyroid diseases are fairly common in pregnancy and their management presents specific challenges. Due to physiological changes in pregnancy, pregnancy-specific reference ranges should be used to assess thyroid function in pregnant women. Given the importance of

normal thyroid function for maternal and child health, both maternal and fetal outcomes should be considered in making management decisions for treatment of thyroid dysfunction in pregnancy. Similarly, the evaluation and treatment of thyroid nodules or thyroid cancer might require special considerations in pregnancy. Thyroid dysfunction is also frequent in the immediate postpartum period.

Many questions related to the care of pregnant women with thyroid disorders remain unanswered. Levothyroxine treatment of maternal subclinical hypothyroidism and hypothyroxinaemia initiated in the second trimester has not shown any benefit; however, it is not known whether levothyroxine treatment initiated earlier in gestation would improve adverse obstetric and child neurodevelopmental outcomes. The mechanism for the observed increased rates of pregnancy loss in TPO-positive euthyroid pregnant women remains unknown; future studies will be needed to determine whether there is an effective therapy for these women. The safest approach to antithyroid drug use for overt hyperthyroidism during gestation is also not entirely clear. Although iodine supplementation for women in mildly-to-moderately iodine-deficient regions is now widely recommended, clinical trials will be needed to determine whether this supplementation improves child developmental outcomes. Furthermore, the appropriate dose and timing of supplementation remains to be elucidated. Regarding thyroid cancer, we do not fully understand the effects of pregnancy on the more aggressive types, such as anaplastic or medullary thyroid cancer. Finally, it is not known whether any intervention could prevent progression of postpartum thyroiditis to permanent hypothyroidism. Additional studies are needed to answer these questions and to further improve the care of women with thyroid disease during gestation and the postpartum period.

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Box 1 |

Risk factors for developing thyroid hypofunction in pregnancy

The risk factors for developing thyroid hypofunction are reviewed in the ATA guidelines[6] and can be summarized as follows:

- History of thyroid dysfunction
- Symptoms or signs of thyroid dysfunction
- Presence of a goitre
- Known thyroid antibody positivity
- Age >30 years
- History of type 1 diabetes mellitus or other autoimmune disease
- History of head or neck radiation or prior thyroid surgery
- Family history of autoimmune thyroid disease or thyroid dysfunction
- Presence of morbid obesity (defined as BMI ≥40 kg/m^2)
- Use of amiodarone, lithium or administration of intravenous contrast agent within the past 3 months
- Two or more prior pregnancies
- History of pregnancy loss, preterm delivery or infertility
- Residing in area of moderate to severe iodine deficiency

Key points

- Serum levels of thyroid stimulating hormone might be lower in pregnant women during early gestation than levels outside the pregnancy setting, due to increased production of thyroid hormone and stimulation from high levels of human chorionic gonadotropin.
- Levothyroxine treatment for maternal subclinical hypothyroidism in pregnancy remains controversial because currently available studies have not shown a clear benefit of treatment on obstetric or child neurodevelopmental outcomes.
- Treatment of Graves disease in pregnancy requires careful consideration of the adverse effects of uncontrolled hyperthyroidism, antithyroid drugs and overtreatment of hyperthyroidism on pregnancy outcomes.
- Women who are planning to be pregnant, are pregnant or are breastfeeding should take a daily oral supplement containing 150 μg of iodine to prevent adverse effects of iodine deficiency.
- Treatment of differentiated thyroid cancer diagnosed in pregnancy can be safely deferred until after pregnancy with close monitoring for any tumour size increase or spread during pregnancy.
- Postpartum thyroiditis is a destructive thyroiditis that typically presents with thyrotoxicosis followed by transient hypothyroidism up to the first 12 months after childbirth.

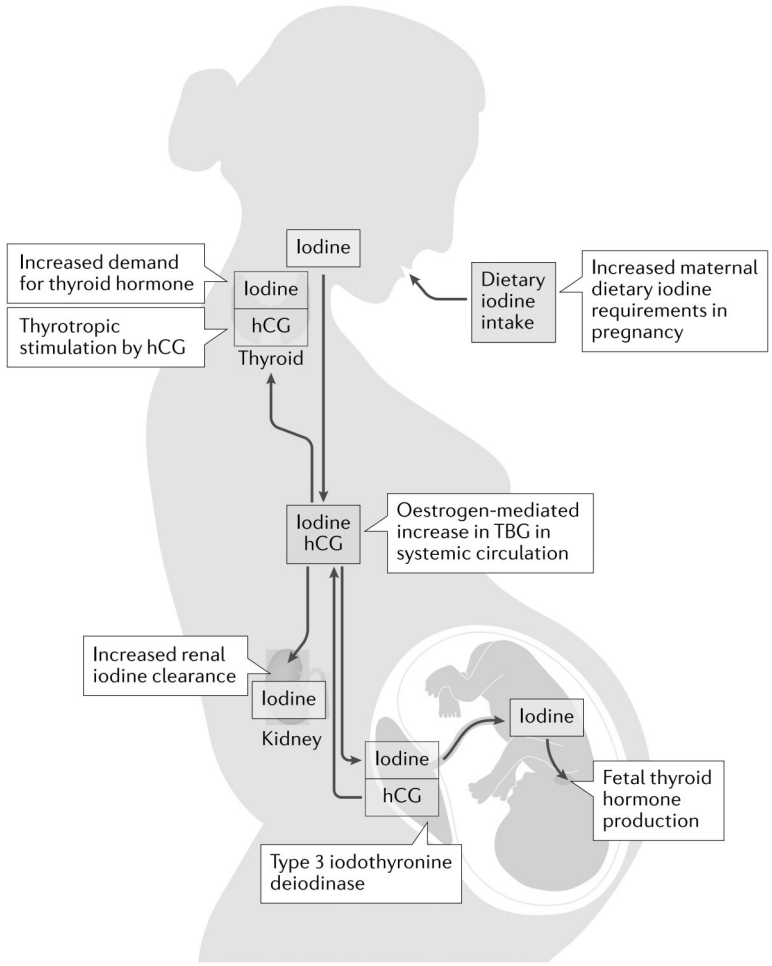

Fig. 1 |. Factors increasing maternal dietary iodine requirement in pregnancy.

Maternal and fetal factors leading to increased iodine requirements in pregnancy are described. During pregnancy, there is a ~50% increase in demand for thyroid hormone, which requires an additional 50–100 μg daily dietary iodine intake. Maternal thyroid hormone production is in part increased by the thyrotropic action of human chorionic gonadotropin (hCG), a hormone produced by the placenta. Oestrogen mediates a twofold increase in circulating levels of thyroxine-binding globulin (TBG), which binds thyroid hormones in the maternal circulation, leading to a relative decrease in levels of active free T_4, which further promotes an increase in thyroid hormone production. Furthermore, placental type 3 iodothyronine deiodinase deactivates T_4 in the circulation to reverse T_3. Increased maternal renal clearance of iodine (by 30–50%) also occurs due to the increase in maternal blood volume. Finally, iodine is transferred from the maternal systemic circulation (red box) to the fetus for fetal thyroid hormone production.

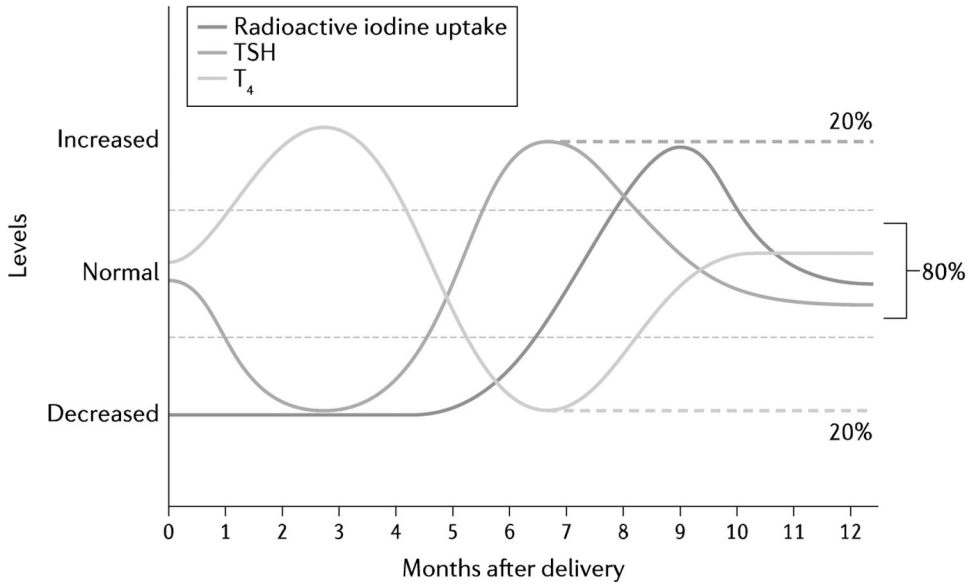

Fig. 2 |. Time course of postpartum thyroiditis.

Typical time course in changes in serum levels of thyroid stimulating hormone (TSH), T_4 and radioactive iodine uptake in postpartum thyroiditis up to 12 months after delivery is depicted. Transient thyrotoxicosis is generally followed by transient hypothyroidism, before full recovery to euthyroidism. However, about 20% of women with postpartum thyroiditis might develop permanent hypothyroidism (as indicated by the dashed lines).

Table 1 |

Current US recommendations for treatment of thyroid hypofunction in pregnancy

Laboratory data	ATA guidelines[6]	ACOC guidelines[13]
TPO antibody-negative and TSH >10 mIU/l	Treat with levothyroxine	Treat with levothyroxine only if free T_4 is low
TPO antibody-positive and TSH greater than the pregnancy-specific range (or >4 mIU/l)	Treat with levothyroxine	Treat with levothyroxine only if free T_4 is low
TPO antibody-positive and TSH >2.5 mIU/l but less than the pregnancy-specific reference range (or <4 mIU/l)	Consider treatment with levothyroxine	No treatment
TPO antibody-negative and TSH greater than the pregnancy-specific range (or >4 mIU/l) but <10 mIU/l	Consider treatment with levothyroxine	Treat with levothyroxine only if free T_4 is low
Isolated hypothyroxinaemia	No treatment	Not discussed

ACOG, American College of Obstetricians and Gynecologists; ATA, American Thyroid Association; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Table 2 |

Recommended daily iodine intakes by life stage

Life stage	Iodine intake (μg per day)
US Institute of Medicine [97]	
Age 0–6 months	110
Age 7–12 months	130
Age 1–8 years	90
Age 9–13 years	120
Age >13 years	150
During pregnancy	220
During lactation	290
WHO [98]	
Age 0–5 years	90
Age 6–12 years	120
Age >12 years	150
During pregnancy	250
During lactation	250

Table 3 |

Median urinary iodine concentration ranges for assessment of population-level iodine status

Croup for assessment	Median UIC (μg/l)	Iodine status
School-age children or non-pregnant, non-lactating adults	<20	Severely insufficient
	20–49	Moderately insufficient
	50–99	Mildly insufficient
	100–299	Adequate
	≥300	Excessive
Pregnant women	<150	Insufficient
	150–249	Adequate
	250–499	More than adequate
	≥500	Excessive

Concentration ranges were obtained from REF.[99] and REF.[159]. UIC, urinary iodine concentration.