Levothyroxine in Pregnancy

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Thyroid hormone homeostasis changes markedly during pregnancy, and first trimester-specific reference ranges for thyrotropin (thyroid-stimulating hormone, TSH) are needed to diagnose hypothyroidism. Treatment consists in levothyroxine (LT4) in this setting (triiodothyronine or desiccated thyroid preparations have no role here). Severe hypothyroidism is associated with infertility, and levels of TSH above 4.0 IU/mL signal an increased risk of adverse pregnancy outcomes. All pregnant women (and women planning a pregnancy) with overt hypothyroidism must be managed effectively with oral LT4. Thyroid autoimmunity increases the risk of adverse pregnancy outcomes and is associated with certain causes of infertility. Current European and US guidelines recommend a role for patients with subclinical hypothyroidism and thyroid autoimmunity, not least to guard against progression to overt hypothyroidism during the pregnancy. Women with hypothyroidism undergoing assisted reproduction technology to become pregnant appear to be strong candidates for LT4-based therapy.

1 Introduction

About 1% of pregnant women have overt hypothyroidism (OH) and about 10% have subclinical hypothyroidism (SCH) during pregnancy [1]. This chapter will address the issue of hypothyroidism in women who are pregnant, planning a pregnancy (with or without assisted reproductive technology [ART]), or who

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are in the immediate postpartum period. Topics to be discussed will include the impact of pregnancy on the management of hypothyroidism, the effects of hypothyroidism and its management with levothyroxine (LT4) on maternal and neonatal outcomes, and the current status of guidelines for the management of these patients.

2 Changes in Thyroid Function During Pregnancy

A number of changes take place due to the presence of the placenta and the foetus [2, 3]. During the first trimester of pregnancy, the foetus is dependent on thyroid hormones of the mother, and at the same time, placental deiodinase type 3 protects it against an excess, by degrading them. Other changes necessitating an increased production of thyroid hormones in the mother are the increased urinary iodine clearance, and thyroxine-binding globulin (TBG) levels due to the higher oestradiol concentrations. This latter phenomenon takes place earlier and is more accentuated if an ovarian hyperstimulation (OS) takes place for a pregnancy conceived using ART. On the other hand, increasing human chorionic gonadotrophin stimulates maternal thyroid to augment thyroid hormone production. Therefore, the thyrotropin level decreases during the first trimester, which partially reverses as the pregnancy progresses [2, 3].

All these changes can lead to the development of (subclinical) hypothyroidism during pregnancy especially where women have severe iodine deficiency, thyroid autoimmunity (TAI), or do not take enough LT4 after thyroid surgery.

Pregnancy markedly increases the dose of LT4 required to control TSH, with changes in LT4 requirement varying according to the aetiology of the hypothyroid state and thyroid status before pregnancy [2–5]. For example, longitudinal studies in pregnant women with hypothyroidism showed that the dose of LT4 needed to control TSH adequately (<2.5 mIU/L) increased by about half during the first trimester and remained relatively stable for the remainder of the pregnancy [6, 7]. This is not a universal finding during pregnancy, however, and a minority of patients in the larger of these studies required no increase in the LT4 dose, and a few even required a dose decrease [6]. Another study, in 19 women, showed that the LT4 dose increased by 47% in the first trimester, and then remained at this level throughout the pregnancy. Current guidelines (see below) recommend an immediate increase in the dose of LT4 when pregnancy is discovered. Postpartum, thyroid function, and LT4 requirements return to pre-pregnancy levels for most patients though some continue to require a higher dose than that received before the pregnancy [6, 8]. In women pregnant after ART, the increase in the LT4 dose is higher and takes place earlier in pregnancy [8]. The presence of TAI is the sole condition that predicts the fact that LT4 will have to be increased during pregnancy, both in spontaneous and assisted pregnancies [6, 9].

3 Maternal and Foetal Outcomes in Women with Hypothyroidism

3.1 *Effects of Hypothyroidism on Fertility and Preterm Delivery*

Severe overt hypothyroidism decreases fertility through its actions on the production of sex hormone-binding globulin (decreased) and prolactin (increased), and via a direct impact on the ovaries [10]. In a meta-analysis of 19 cohort studies (involving a total of 47,045 pregnancies), SCH was associated with an increased risk of preterm delivery, with an odds ratio (OR) 1.04 (95%CI, 1.00–1.09) for each increase in TSH of one standard deviation [11]. The presence of antibodies to thyroid peroxidase also increased the risk of preterm delivery in this study (OR 1.33; 95%CI, 1.15–1.56). In women with iodine deficiency (urinary iodine <100 µg/L) TSH $\geq$ 4.0 mIU/L was associated with a 2.5-fold ($p = 0.024$) increased risk of preterm delivery, compared with lower TSH levels, in the population-based Tehran Thyroid and Pregnancy Study [12]. In another study, inadequately controlled hypothyroidism was associated with an increased risk of miscarriage, especially where TSH level exceeded 4.5 mIU/L [13].

3.2 *LT4 Treatment and Pregnancy Outcomes: Importance of Thyroid Autoimmunity*

A placebo- (or no treatment-) controlled evaluation of LT4 in pregnant women with overt hypothyroidism would be unethical, given the known association of markedly elevated TSH with miscarriage [14]. Overt hypothyroidism should always be treated with LT4 during pregnancy, as in other settings [14].

Most evidence relating to the effects of LT4 on pregnancy outcomes has come from clinical studies in women with SCH. A randomised trial in 64 infertile women with SCH undergoing in vitro fertilisation (IVF) and intracellular sperm injection (ICSI) found a higher embryo implantation rate and live birth rate, associated with a lower miscarriage rate, in subjects randomised to LT4 vs. no LT4 [15]. The study population was not selected for the presence of TAI *per se* though higher anti-TPO and anti-Tg levels predicted a higher risk of miscarriage in the control group. The potential influence of TAI on pregnancy outcomes in LT4-treated women undergoing ICSI is discussed in more detail later in this chapter.

A meta-analysis of 13 randomised and observational studies included more than 11,000 women with SCH [16]. Treatment vs. no treatment with LT4 in this analysis affected different pregnancy outcomes in different ways, with fewer lost pregnancies (OR 0.78; 95% CI 0.66–0.94) and more live birth rates (OR 2.72; 95% CI 1.44–5.11), but a higher chance of premature labour (OR 1.82; 95% CI 1.14–2.91).

Increasing the dose of LT4 for women with TSH >2.5 mIU/L in the first trimester was also associated with a ~ 15 -fold reduction in the frequency of preterm birth, compared with pregnant women whose LT4 dose remained stable, according to a retrospective analysis [17]. However, there appeared to be no upper limit for TSH in this study, and the median TSH level before the LT4 dose increase was 5.0 mIU/L.

The appearance of TAI is also strongly associated with certain causes of infertility, in particular polycystic ovary syndrome and idiopathic infertility [10]. Numerous studies have addressed the impact of TAI on pregnancy outcomes, following the initial finding of a two-fold increase in the risk of miscarriage associated with anti-TPO-Ab and/or anti-Tg-Ab three decades ago [18]. Meta-analyses have confirmed these initial findings consistently, with odds for miscarriage ratios of 2.31 (cohort studies in women with vs. without TAI) [19], 2.55 (case-control studies from the same meta-analysis) [19], 2.8 (women with vs. without SCH or TPO-Ab who had undergone ART [20], 3.9 (cohort studies of euthyroid women with vs. without TAI) [21], 1.8 (case-control studies from the same meta-analysis), 21 and 1.44 (women with vs. without TAI undergoing ART) [22]. Furthermore, a recent (retrospective) analysis demonstrated a 17-fold increase in the requirement for neonatal intensive care treatment associated with TAI [23].

Two recent meta-analyses in both spontaneous and assisted pregnancies have appeared recently, from the same group published one year apart (2018–2019), finding that treatment with LT4 was associated with less pregnancy loss and fewer preterm births in women with SCH and TAI [24, 25]. A further meta-analysis (14 randomised or observational trials) focussed on women with SCH and/or TAI and found that LT4 vs. placebo or no treatment was associated with reduced risk of a range of adverse outcomes (higher fertilisation and delivery rates, lower rates of miscarriages, gestational diabetes, and gestational hypertension, preterm deliveries, and low birth weights) [26].

A prospective study compared the effects of LT4 vs. no treatment on pregnancy outcomes in 131 patients with SCH (TSH could be as high as 10 mIU/L) and TPO-Ab [27]. LT4 treatment was associated with fewer preterm deliveries vs. no treatment or a euthyroid, TPO-Ab–control group. Finally, a report from the Tehran Thyroid and Pregnancy Study described randomisation of 366 pregnant women with SCH (TSH cut-off 2.5 mIU/L), but no TPO-Ab, to LT4 or no treatment [28]. LT4 did not affect the risk of adverse pregnancy outcomes. Interestingly, there was a significant reduction for LT4 vs. no treatment for preterm delivery for patients with TSH >4.0 IU/L.

Accordingly, the results of clinical studies in women with SCH have been conflicting, with regard to the effects of LT4 on pregnancy outcomes. This might be due to the use of TSH >2.5 mIU/L as cut-off to define SCH during the period 2005–2016. Most studies defining SCH as a TSH >4.0 mIU/L or above the upper limit of the reference range for non-pregnant women show beneficial effects of LT4 on pregnancy outcomes.

3.3 LT4 Treatment of Euthyroid Women with Thyroid Autoimmunity

Two randomised trials have been conducted in euthyroid women with TAI. The Thyroid Antibodies and Levothyroxine study (TABLET) randomised 952 women with TPO-Ab and a history of miscarriage or infertility to treatment with LT4 50 µg or placebo from before conception to the end of the pregnancy. There were no differences between groups in the live birth rate (primary outcome) or the number of miscarriages [29]. In an earlier (2006), smaller, randomised trial in women with TPO-Ab not selected for the presence of thyroid dysfunction, treatment with LT4 was associated with a lower miscarriage rate, compared with no LT4 treatment [30].

Other evidence in this area is from meta-analyses and observational studies. One meta-analyses demonstrated no marked effect of LT4 supplementation on pregnancy outcomes in euthyroid women with TAI [31]. Administration of LT4 of women with loss of at least two prior pregnancies and TSH 2.5–4.0 mIU/L did not influence the success of a subsequent pregnancy significantly, and TPO antibody status did not modify this finding, in an observational study [32]. On the contrary, in a recent large cohort of women with unexplained recurrent pregnancy loss, TPO-Ab positivity was predictive of a reduced live birth rate, and furthermore, LT4 improved odds of live birth [33]. More randomised controlled trials are needed to resolve this issue.

An additional case-control study found no dose-related effect of LT4 treatment on pregnancy outcomes, compared with an untreated control group, in euthyroid women without TAI, despite significant changes in placental function markers [34]. These data support the current recommendation that euthyroid women without TAI, including those with high-normal TSH levels, may not require intervention with LT4 treatment (see below). A single-centre, cross-sectional analysis of 1321 women without thyroid disease showed that variation of the TSH level within normal range for non-pregnant women did not increase the risk of adverse pregnancy outcomes, including gestational diabetes, pre-eclampsia, postpartum haemorrhage, intra-uterine growth retardation, or low birth weight [35].

3.4 Thyroid Autoimmunity and Pregnancy Outcomes in Women Receiving Assisted Reproduction Technologies (ART)

Thyroid autoimmunity is common among women seeking treatment for infertility: one study of detected thyroid autoantibodies in 16% of an unselected cohort women attending specialist care for this reason [36]. The majority (12%) had anti-TPO-Ab ± anti-thyroglobulin antibodies (anti-Tg-Ab), and 5% had only anti-Tg-Ab. However, most studies in this area have been based on detection of anti-TPO-Ab, which is more often measured routinely [14].

Fig. 1 Effects of LT4 on pregnancy outcomes from a meta-analysis of studies in women with subclinical hypothyroidism undergoing assisted reproduction. Risk ratios >1 signify higher likelihood of event in the levothyroxine vs. control group; *p* values are for overall effect. (Drawn from data presented in Ref. [24])

Observations of increased miscarriage rates associated with TAI (see above) have prompted evaluations of LT4 in euthyroid women with anti-thyroid antibodies receiving ART. Another study found that randomisation of such a population to LT4 (25 µg [TSH <2.5 mIU/L] or 50 µg [TSH ≥2.5 mIU/L]) vs. placebo had no significant effect on miscarriage rates (primary outcome) or on clinical pregnancy rates or live birth rates (secondary outcomes) [37]. An accompanying editorial welcomed the study, but noted its relatively low miscarriage rate, compared with other, similar populations, and the relatively low proportion of pregnancies achieved using ICSI about half [38]. Moreover, previous neutral evaluations of LT4 in similar populations were underpowered and/or non-randomised [30, 39].

A recent meta-analysis of 765 pregnancies achieved using ICSI showed that the rate of miscarriage in these women was unaffected by TAI [40]. This is an opposite result compared with previous meta-analyses on the impact of TAI on pregnancy outcomes, as described above. More studies are needed to find out whether this is due to the use of ICSI or because studies were included that used a cut-off for TSH of 3.0 mIU/L (or lower) to define SCH. An argument in favour of the latter hypothesis is a meta-analysis from Velkeniers et al. (published in 2013), in which LT4 treatment vs. no additional treatment decreased the miscarriage rate and increased the live birth rate in women with SCH (defined by TSH levels >4.0 mIU/L) achieving pregnancy through ART (Fig. 1) [20]. However, no beneficial impact of LT4 was noted in women with TAI undergoing ART in a more recent meta-analysis in which SCH was defined in the majority of included studies by TSH <4.0 mIU/L [24].

ICSI and LT4 may work together to improve outcomes especially when ICSI is used to assist conception: ICSI may bypass inhibitory effects of thyroid antibodies in the follicular fluid that surrounds the ovum, while LT4 preserves a more normal hypothalamic-pituitary-thyroid axis after implantation [38].

A cross-sectional study in 279 women undergoing ART found that either TSH above vs. below 2.5 mIU/L in women without TAI, or the presence vs. absence of TPO-Ab, did not affect the quality of oocytes retrieved, the fertilisation rate or the

quality of the subsequent embryos [41]. Further studies are needed, to investigate whether LT4 could improve the ovarian reserve or in vitro outcomes of an ART procedure.

3.5 *Effects on Offspring*

Cognitive outcomes in children born to mothers with hypothyroidism is also an active area of research. Low T4 levels in mothers have been associated significantly with delayed cognitive development in their children in some [42, 43] but not all [44] studies. A meta-analysis, of three randomised trials conducted in women diagnosed with SCH during pregnancy, found no effect of LT4 treatment on children's neuropsychological outcomes [45]. Treatment of hypothyroid mothers in the second trimester did not improve neurocognitive outcomes in the offspring [46]. A follow-up study to the Tehran Thyroid and Pregnancy Study will evaluate the neurocognitive development of 3-year old children born to mothers with mild hypothyroidism (without TAI) [47].

4 Summary of Current Major Guidelines

4.1 *Guidelines Considered Here*

Guidelines from Europe (on subclinical hypothyroidism) [48] and the USA (a broad guideline considering most aspects of hypothyroidism [14]) will be considered here, as examples of major guidelines with international reach. Many other guidelines are available for other regions: it is beyond the scope of this chapter to review them all, and chapter, "Practical Application of Levothyroxine-Based Therapy" of this book lists a number of them.

4.2 *Overt Hypothyroidism During Pregnancy and Postpartum*

The American Thyroid Association (ATA) published a major guideline on the management of thyroid disease in 2017 [14]. This comprehensive guidance covered all aspects of thyroid dysfunction and stated 109 clinical questions that were answered by 111 recommendations. Table 1 provides an overview of these recommendations, grouped under convenient subheadings, and a brief description of the main points with regard to LT4 therapy follows.

Briefly, diagnosis of maternal hypothyroidism should be conducted using trimester-specific reference ranges for TSH, ideally specific to a particular assay

used, and defined in local, healthy, euthyroid, pregnant women without TPO-Abs. Depending on these factors, serum TSH values defining SCH during the first trimester will be >3.5–4.5 mIU/L. Measurement of TSH is recommended regularly for women at risk of thyroid disease (e.g. due to TAI or SCH). General screening for elevated TSH is not supported for women at low risk for thyroid disease, with the exception of women undergoing ART.

Table 1 Overview of principal recommendations from the American Thyroid Association regarding the management of hypothyroidism during pregnancy

Measure TSH	<ul style="list-style-type: none"> • In women under care for infertility • At start of pregnancy, and every 4 weeks through mid-pregnancy and at least once near 30 weeks gestation in women with thyroid Abs • <i>Measure TSH 2 weeks after controlled ovarian stimulation during ART, as this renders test results difficult to interpret (repeat at 2–4 weeks if TSH is high)</i> • <i>No support for universal screening for abnormal TSH in women without risk factors for thyroid disease (except for those planning ART)</i>
Diagnosis	<ul style="list-style-type: none"> • Maternal hypothyroidism = TSH > upper limit of trimester-specific reference range • Use assay-specific reference ranges (if possible locally derived from healthy, I-replete, TPO-Ab—pregnant women without thyroid illness) • Use an upper reference limit of ~4 mIU/L where such reference ranges are not available • TT4 measurement is a suitable alternative to FT4 later in pregnancy
Iodine and other supplements	<ul style="list-style-type: none"> • Use median urinary iodine concentrations, not spot or 24 h measurements to determine iodine status in an individual • Pregnant women need ~250 µg iodine/day, usually via a potassium iodide supplement (<i>an annual dose of iodised oil is a temporary solution for some I-depleted low-resource areas</i>) • No need for iodine supplementation if a woman is taking LT4 • Avoid excessive iodine exposure during pregnancy (except pre-surgery for Graves' disease) due to concerns about causing hypothyroidism in the foetus • Breastfeeding women should take iodine supplementation (similar to above; all breastfeeding women should ingest a ~250 µg iodine/day)
Use of LT4 during pregnancy	<ul style="list-style-type: none"> • Counsel hypothyroid women of an increased requirement for LT4 during pregnancy: if pregnancy occurs, they should increase their LT4 dose by about 20–30% and contact/see their physician promptly • Use oral LT4 for all women with overt hypothyroidism who are planning pregnancy, or during pregnancy; <i>aim for lower half of trimester-specific reference range for TSH (or TSH <2.5 mIU/L)</i> • There is insufficient evidence for routine use of LT4 for women with subclinical hypothyroidism without thyroid autoimmunity who are trying to become pregnant—but, LT4 may be considered as it may prevent progression to overt hypothyroidism • Do not use LT4 + T3 or desiccated thyroid preparations • <i>Consider LT4 for TPO-Ab + women with prior recurrent idiopathic pregnancy loss</i> • <i>Do not routinely treat isolated hypothyroxinaemia (low FT4 with normal TSH)</i> • Maintain TSH at the preconception level for pregnant women with thyroid cancer

Table 1 (continued)

Postpartum	<ul style="list-style-type: none">• Reduce LT4 dose to the preconception level after delivery, check TSH ~6 w postpartum (some women do not need LT4 postpartum, especially where the dose was <50 µg)• Check thyroid status for otherwise unexplained lack of milk production• Treat hypothyroidism irrespective of severity in women seeking to breastfeed• TSH measurement to follow course of postpartum thyroiditis (PPT; including annually in women with prior PPT) and <i>consider LT4 for the hypothyroid phase (discontinue LT4 by ~12 months in the absence of new pregnancy)</i>• Do not use LT4 to prevent PPT in euthyroid, Ab+ pregnant women
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Selected recommendations relating to the management of overt hypothyroidism are summarised here; these have been paraphrased, and in some cases aggregated, for brevity: see the full guideline. “Weak” recommendations are shown in italics; others are “Strong”. Compiled from information presented in Ref. [14]

Oral LT4 is the mainstay of treatment of overt hypothyroidism during or leading up to a pregnancy, as for other populations with hypothyroidism. The guideline strongly recommends against the use of LT4 + LT3 combinations, or the use of desiccated thyroid preparations for treatment, a practice, which continues in spite of a lack of evidence of benefit, an evidence for harm, during pregnancy [49]. In general, targeting the lower half of the TSH reference range is supported for women with hypothyroidism who are, or who are planning to become pregnant. Women should be educated on the likelihood of a steep rise in LT4 requirement during pregnancy and should be ready to increase their LT4 dose on discovering a pregnancy *before* seeking prompt advice from their healthcare team. In daily practice, this could be implemented by adding two LT4 tablets a week at confirmation of the pregnancy [50]. LT4 requirements decrease postpartum, sometimes to zero, especially where the maintenance dose during pregnancy was low (<50 µg).

LT4 treatment may be considered also for the management of the hypothyroid phase of postpartum thyroiditis (PPT), which classically follows a transient hyperthyroid phase and occurs from 3 to 12 months postpartum. Indications to treat are women with symptomatic hypothyroidism and/or TSH values >10 mIU/L. In 10–20% of the cases, the hypothyroidism can be permanent, depending on pre-existing thyroid dysfunction (elevation of TSH and TPO-Ab levels). In most women, the duration of LT4 therapy, once initiated, is uncertain. It is reasonable to start weaning patients off treatment after 6–12 months of treatment, in the absence of a new pregnancy or decision to breastfeed [14].

It is important to note that LT4 treatment does not prevent PPT. Finally, oral LT4 may be considered for hypothyroid women who lack milk production, once other possible causes have been excluded. Breastfeeding *per se* is not a contraindication to LT4 treatment.

The ATA guidance considered that there was insufficient evidence to support the use of LT4 with the intention of preventing pregnancy loss, for euthyroid women with TAI, a position that is likely to be strengthened by the recent results of the TABLET study, described above. However, a weak recommendation supports the administration of a low dose of LT4 (typically starting at 25–50 µg) to women with TAI undergoing ART, given the possibility of benefit vs. minimal risk. One more

indication (not as yet in the ATA guidance) could be women with recurrent idiopathic miscarriage and TAI (see above) [33].

A guideline on the management of SCH from the European Thyroid Association (ETA), published in 2014 [48], contains some recommendations on the management of overt hypothyroidism. These are in general compatible with the ATA guideline. In particular, this guideline agreed with the later ATA guidance on:

- The use of LT4, rather than combination therapy or desiccated thyroid products.
- The principle of managing TSH to the lower half of its trimester-specific reference range.
- The return to the preconception dose of LT4 postpartum.

The ETA guideline differs from the ATA guideline in providing low-strength support for the use of LT4 for managing isolated hypothyroxinaemia in the first trimester, on the basis of an association of this condition with neuropsychological impairment on the neonate.

Other guidance summarised in Table 1 concerns the maintenance of adequate iodine intake. This is included for completeness and will not be discussed further here. Similar recommendations are provided in the ETA guideline for SCH (see the full guideline for details) [48].

4.3 Subclinical Hypothyroidism During Pregnancy and Postpartum

The principal sources of guidance for the management of SCH are from the 2014 guideline from the ETA [48] and the 2017 ATA guideline, described above for the management of overt hypothyroidism [14].

The ETA guideline notes the likely association between SCH and a range of adverse pregnancy outcomes (pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia, and preterm delivery), while acknowledging the conflicting results of some of these studies (see above). Accordingly, the ETA guideline supports treating women diagnosed with SCH before and during pregnancy with oral LT4 (Table 2). Both the ETA and ATA guidelines provide stronger recommendations on the use of oral LT4 treatment for women who are TPO-Ab+ (Table 2). The ATA guideline further supports LT4 treatment of women with SCH who are receiving ART or are breastfeeding (Table 2).

No recommendation was provided on screening for SCH was made by the ETA, due to a lack of evidence, consistent with the views of the ATA, discussed above. The authorship was split on this issue, however, with some authors noting that such an approach would avoid the danger of pregnancies being exposed to undiagnosed overt hypothyroidism. This uncertainty has been reflected in clinical practice, where survey evidence identified marked differences within Europe with respect to screening for hypothyroidism in pregnancy [51]. The ATA guideline noted that prevention of progression to overt hypothyroidism is an advantage of detecting SCH early in the pregnancy.

Table 2 Comparison of European and US guideline recommendations on the use of LT4 to manage subclinical hypothyroidism in pregnant women, or women planning a pregnancy

Patients	ETA recommendations (2014)	ATA recommendations (2017)
TPO-Ab+	<p>Recommends use of oral LT4 to maintain TSH <2.5 mIU/L in women planning pregnancy, especially those who are TPO-Ab+ (level 2 recommendation)</p> <p>Recommends use of oral LT4 for women with newly diagnosed subclinical hypothyroidism to control TSH to within its trimester-specific reference range (no recommendation level provided)</p>	<p>Recommends use of oral LT4 where TSH is above the trimester-specific reference range (strong recommendation)</p> <p>Consider use of oral LT4 where TSH is between 2.5 mIU/L and the top of the trimester-specific reference range (weak recommendation)</p>
TPO-Ab–	<p>Recommends use of oral LT4 to maintain TSH <2.5 mIU/L for women with subclinical hypothyroidism (level 2 recommendation)</p> <p>Stop LT4 after pregnancy if TSH <5 mIU/L (level 2 recommendation)</p>	<p>Recommends use of oral LT4 where TSH is >10 mIU/L (strong recommendation)</p> <p>Consider use of oral LT4 where TSH is between 2.5 and the 10 mIU/L (weak recommendation)</p> <p>Do not use LT4 where TSH is within the trimester-specific reference range (strong recommendation)</p>
Assisted reproduction	–	Recommends use of oral LT4 to reduce TSH to below 2.5 mIU/L in women with SCH undergoing in vitro fertilisation or intracytoplasmic sperm injection (strong recommendation)
Breastfeeding	–	Treat subclinical hypothyroidism in women wishing to breastfeed postpartum (weak recommendation)

Recommendations are abbreviated and paraphrased for clarity: see the full guidelines. *SCH* subclinical hypothyroidism, *TSH* thyrotropin, *TPO-Ab* anti-thyroid peroxidase antibody. Compiled from Refs. [14, 48]

5 Conclusions

Overt hypothyroidism must be managed effectively with oral LT4 during pregnancy, with increases in the dose made to match the changing requirements for LT4 as the pregnancy progresses. The management of subclinical hypothyroidism remains a matter for debate and further research. Clear and consistent evidence for improved pregnancy outcomes with LT4 in thyroid Ab-negative women is scarce. The presence of thyroid autoimmunity increases the risk of adverse pregnancy outcomes and is strongly associated with some causes of infertility. LT4 therapy may have a role in these patients especially those undergoing a hyperstimulation protocol as part of ART. Emerging evidence suggests that ICSI may be a particularly suitable mode of ART for women receiving LT4 for autoimmune hypothyroidism.

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