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REVIEW

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# Thyroid hormone therapy of hypothyroidism in pregnancy

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**Abstract**
Hypothyroidism is the most frequent pregnancy-related thyroid dysfunction, including overt and subclinical hypothyroidism. Studies show that even mild hypothyroidism may eventuate in adverse gestational outcomes and intellectual impairment of offspring. Women with overt hypothyroidism (OH) must be treated by levothyroxine (LT4) pre- and during pregnancy, however, it is controversial that when and how to initiate LT4 therapy and further optimize dosing so that pregnant women and their offspring may truly benefit. In the review we will analyze the changes in thyroid hormone requirements in pregnant women, the timing of LT4 treatment and adjustment of LT4 dose according to etiology in patients with hypothyroidism during pregnancy, and adjustment of LT4 after delivery.

**Keywords** Pregnancy · Hypothyroidism · TSH · FT4 · Levothyroxine

## Introduction

Hypothyroidism is the most common thyroid dysfunction during pregnancy and is a serious health issue. Even mild degrees of gestational hypothyroidism carry higher risk of miscarriage, preterm delivery, low birthweight, fetal death, or neurointellectually impaired offspring. LT4 replacement is a safe and effective treatment strategy to minimize maternal and fetal harm in this setting. Appropriate dosing at the earliest opportunity is essential so that targeted levels of thyroid function are reached.

## Diagnosis and epidemiology of hypothyroidism in pregnancy

### Diagnosis of hypothyroidism in pregnancy

Generally speaking, both overt and subclinical degrees of insufficiency qualify as gestational hypothyroidism. The diagnosis is determined by gestation-specific reference ranges of circulating TSH, FT4, and total thyroxine (TT4) [1–3]. Although not always at hand, these parameters offer the best chance of diagnostic accuracy. The 2017 American Thyroid Association (ATA) guidelines stipulate that in the absence of pregnancy-specific TSH reference range, an upper limit of 4.0 mU/L may be used as the cut-point for pregnant women [1]. According to one Chinese meta-analysis of gestation-specific reference ranges provided in five assay kits, the upper limit of serum TSH in the first trimester is 22% lower than the corresponding non-pregnant upper limit. Furthermore, the value is very close to 4.0 mU/L. Thus, a cut-point of 4.0 mU/L is quite suitable for diagnosing first-trimester gestational hypothyroidism in pregnant Chinese women [4].

### Prevalence of overt hypothyroidism and subclinical hypothyroidism in pregnancy

Factors such as serum TSH threshold, stage of pregnancy, and regional iodine nutritional variations may influence the prevalence of gestational hypothyroidism. Still, subclinical hypothyroidism typically exceeds overt hypothyroidism in this regard. Only 2.4% of a maternal population with known TSH elevations during pregnancy met the diagnostic criteria for overt hypothyroidism, whereas subclinical hypothyroidism accounted for 97.6% [5].

Based on gestation-specific serum TSH and FT4 reference ranges in iodine-sufficient regions, the prevalence of

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overt hypothyroidism in the first half of gestation is 0.2–0.9%, compared with 2.3–4.0% for subclinical hypothyroidism [6–9]. Whether invoking a standard TSH cut-point of 2.5 mU/L or the gestation-specific serum TSH threshold of 3.67 mU/L, the prevalence of overt hypothyroidism during early pregnancy is scarcely affected (0.76% vs. 0.75%, respectively) [9]. On the other hand, the prevalence of subclinical hypothyroidism surges dramatically, climbing from 4% to 27.8% [7, 9].

By applying unified diagnostic criteria, it is clear that TSH elevation in the first trimester is more prevalent than in second trimester (14.8% vs. 9.2%) [10]. This particular phenomenon is similarly observed in studies of other ethnicities (Dutch: 15.5% vs. 9.5%; Surinamese: 17.9% vs. 5.8%) [10].

Differences in iodine intake have marginal effects on the prevalence of overt hypothyroidism but are critical in the prevalence of subclinical hypothyroidism. As gestation-specific TSH and FT4 diagnostic criteria are increasingly adopted, a significantly greater risk of subclinical hypothyroidism has become evident in regions of excessive (20%) vs. adequate (2.3%) iodine intake [11].

### Causes of hypothyroidism in pregnancy

In iodine-sufficient regions, chronic autoimmune thyroiditis is the most common precursor to overt hypothyroidism. Other precipitating events include subtotal or total thyroidectomy and radioactive iodine therapy. Unlike overt hypothyroidism, thyroid autoantibodies (to thyroid peroxidase [TPOAb] or thyroglobulin [TgAb]) are not major factors in subclinical gestational hypothyroidism, occurring at a 28% rate [12]. Iodine intake that is more than adequate or excessive in nature is the likely basis for subclinical hypothyroidism, because chronic iodine excess seems to elevate serum TSH levels [11, 13, 14].

## Changes in thyroid hormone requirements during pregnancy

Both maternal and fetal demands for thyroid hormones increase during pregnancy. In healthy pregnant women, production and secretion of endogenous thyroid hormone rise through the self-regulated hypothalamic-pituitary-thyroid axis. This begins at 4–6 weeks of gestation and increases gradually, stabilizing at 20 weeks and remaining so until delivery [1].

During the first trimester, an upsurge in human chorionic gonadotropin (hCG) stimulates the thyroid gland to synthesize and secrete thyroid hormone. FT4 then increases to a degree, thus limiting pituitary TSH secretion through negative feedback and depressing serum TSH in turn. The upper limit of TSH is subsequently lowered by about 20–30%, relative to the non-pregnancy threshold [15]. In the second and third trimesters, thyroidal stimulation is weaken as the hCG level falls, and serum FT4 concentration is gradually lower. However, a rise in thyroxine-binding globulin (TBG) begins at week 6 of gestation and reaches plateaus at 16 weeks. Bound T4 increased as a consequence, resulting in elevated serum TT4 and declining FT4 concentration. The thyroid gland must then produce more thyroid hormone to sustain serum FT4 levels. In the second and third trimesters of pregnancy, placental type 2 (D2) and type 3 (D3) deiodinase activities increase, converting T4 into T3 and reverse T3 (rT3), and again serving to reduce serum FT4 level.

The thyroid gland is incapable of timely adjustments to the heightened demand for thyroid hormone manifested in pregnant women with hypothyroidism. Exogenous LT4 dosing is required. It should be noted that autoantibodies (TPOAb/TgAb) may attenuate the stimulatory effect of hCG on FT4 and its suppression of TSH [16, 17]. Iodine is the raw material used to synthesize thyroid hormone, so moderate or severe iodine deficiency may lower FT4 levels; and iodine excess may have the same effect [18]. Thyroid peroxidase (TPO) is a ferriferous enzyme essential in the synthesis of thyroid hormone. TPO activity is diminished in states of iron deficiency, thereby reducing serum levels of FT4 [19, 20]. Ultimately, the impact of above fluctuations on levels of TSH and FT4 will influence exogenous LT4 dosing.

## The role of maternal thyroid hormone in pregnancy

It has long been assumed that maternal thyroid hormone does not cross the placental barrier, insulating fetal growth and development (especially the brain) from its effects. Not until the late 1980s did Vulsma et al. eventually discover T4 in the cord blood and serum of newborns with severe hypothyroidism (thyroid agenesis or total iodide organification defect). They further estimate that the maternal-to-fetal ratio of serum T4 is roughly 3:1, thus dispelling traditionally held views [21].

Thyroid hormone derived from both mother and fetus is essential for fetal brain development. The fetal thyroid gland forms at week 12 of gestation and becomes increasingly functional later [22]. Prior to week 12, the fetus depends entirely on the mother for thyroid hormone. That dependency slowly dissipates after week 20 of gestation. Only 10% of thyroid hormone at term is maternal in origin.

Past studies have underscored the cerebral prioritization of thyroid hormone and the selectivity for T4 during development of the brain [23]. Concentrations of T4 and T3

in fetal cortex increase substantially, mirroring serum levels of T4 but not those of T3. Serum T3 concentrations remain quite low in the fetus, indicating that cortical T3 is generated through D2 catalytic conversion of T4. Adequate maternal T4 is therefore critical for normal fetal brain development [23, 24]. Indeed, this principle has been verified in case-controlled clinical studies [25, 26].

Such studies have also revealed that in pregnant women with subclinical hypothyroidism, the intelligence of their offspring may be adversely affected, even if FT4 is normal and TSH alone is elevated [27, 28]. Basic research has shown that FT4 utilization in embryonic or fetal tissues is reduced, despite normal levels of maternal FT4, signaling insufficient FT4 for proper fetal brain development [24]. Animal experiments have similarly indicated that learning and memory capacity are compromised in offspring of female mice with subclinical hypothyroidism [29].

In conclusion, FT4 may be normal in pregnant women with subclinical hypothyroidism, but TSH elevation reflects low thyroid functional reserve. This poses a threat to fetal brain development and intelligence level, stemming from lack of T4. Comparatively more maternal T4 is clearly needed in this setting to satisfy fetal demands.

## Treatment of hypothyroidism in pregnancy

### Choice of medication for hypothyroidism in pregnancy

As already discussed, maternal T4 (rather than T3) plays a key role in fetal brain development during pregnancy. LT4 is thus the preferred remedy for hypothyroidism in pregnancy. Levotriiodothyronine (LT3), T3/T4 in combination, and desiccated thyroid tablets are not advocated.

Thyroid hormones may be transported across the placenta via monocarboxylate transporter 8 (MCT8) and organic anion-transporting polypeptide 1c1 (Oatp1c1) carrier proteins [30]. According to Vulsma et al., maternal thyroxine does traverse the placenta and reach the fetus [21]. There are also placental deiodinases (D2, D3) to ensure that amounts of T3/T4 passed from mother to fetus are appropriate.

### LT4 treatment for overt hypothyroidism in pregnancy

Women with overt hypothyroidism who contemplate pregnancy must first normalize TSH and thyroid hormone levels through LT4 replacement therapy. ATA guidelines specify a pre-pregnancy serum TSH level <2.5 mU/L [1]. If TSH is held to <1.5 mU/L, the risk of mild hypothyroidism is further reduced in early pregnancy. At TSH levels <1.2 mU/L, the proportion of patients requiring increased doses of LT4 during pregnancy is lowered [31]. For patients with post-thyroidectomy hypothyroidism, adjusting LT4 doses to the lower quartile of normal reference range prior to pregnancy is a safe and effective means of maintaining normal thyroidal function during pregnancy [32].

Once pregnant, these women should promptly undergo thyroid function tests and screening for autoantibodies to gauge LT4 dose adjustments. If there is overt hypothyroidism due to thyroid failure, hCG-induced synthesis of thyroid hormone and compensation for bound T4 is no longer feasible. An increase in exogenous LT4 is then obligatory to meet the heightened gestational demand for thyroid hormone.

In women under treatment for hypothyroidism, LT4 dosing should be increased by 20–50% at the onset of pregnancy [33–36]. Consensus guidelines suggest that the simplest approach is an extra two doses weekly, instituted as early as possible to avoid hypothyroidism [1]. However, one particular study has found that two empiric doses are more likely to overly suppress TSH in the first trimester. Gradual dose adjustments may be best to maintain acceptable levels of TSH during pregnancy [37].

The etiology of hypothyroidism is an important consideration in LT4 replacement therapy. Patients with overt hypothyroidism after thyroidectomy and radioiodine ablation therapy require more LT4 than those with hypothyroidism due to autoimmune thyroiditis. Verga et al found that most patients (86.5%) require higher LT4 dosing during pregnancy. The optimal timing was in first trimester, using increments of 22.9 ± 9.8 μg/day. Once TSH levels stabilized at 0.5–2.5 mU/L, final LT4 dosages in pregnant women with hypothyroidism were as follows: subclinical, 101.0 ± 24.6 μg/day; overt, 136.8 ± 30.4 μg/day; or postablative, 159.0 ± 24.6 μg/day. Compared with pre-pregnancy dosing, administration of LT4 increased by 70%, 45%, and 49%, respectively [35]. In patients with thyroid cancer whose serum TSH is suppressed, minimal LT4 dosing is required to augment levels during pregnancy [38]. Other pertinent factors, such as pre-pregnancy TSH levels and body weight, may also impact LT4 replacement doses.

For overt hypothyroidism that is newly diagnosed during pregnancy, the LT4 replacement dose may be as high as 2.0–2.4 μg/kg body weight per day, which is 25–50% higher than levels used in the general population (1.6–1.8 μg/kg body weight). A retrospective analysis of patients with overt hypothyroidism during pregnancy has shown that at target TSH levels <2.5 mU/L (in first trimester) and <3 mU/L (in second trimester), an initial LT4 dose of 2.33 ± 0.59 μg/kg/day enabled 76.92% of patients to reach TSH target levels by 5.3 ± 1.8 weeks. In addition, there was no significant difference between initial and final doses (initial dose, 133.44 ± 16.46 μg/day) [39]. In patients

with severe hypothyroidism, twice the replacement dose should be given within a few days after starting treatment, thereby expediting normalization of the extrathyroidal T4 pool [1]. Patients who have heart disease are subject to dosage increases as tolerated.

ATA guidelines also cite a target TSH level of less than one-half the gestation-specific reference range or <2.5 mU/L to address maternal hypothyroidism [1]. Changes in LT4 dosing during pregnancy should be adjusted over time, based on serum TSH treatment goals. By testing thyroid function every 4 weeks, 92% of abnormalities are detectable, compared with 73% at 6-week intervals [33].

In women previously diagnosed with hypothyroidism, increased demand for thyroid hormones during pregnancy is for the gestational period only. Postpartum LT4 doses should be reduced to pre-pregnancy levels. For overt hypothyroidism diagnosed during pregnancy, LT4 dosing used in non-pregnant states may be given postpartum. The serum TSH level must be reviewed 6 weeks after delivery to allow LT4 dosage adjustments.

## LT4 treatment for subclinical hypothyroidism in pregnancy

There is lingering controversy over treatment of SCH diagnosed during pregnancy, questioning whether LT4 intervention may help limit adverse pregnancy outcomes and improve intelligence levels of offspring. Pregnant women who are TPOAb negative and have TSH levels of 2.5–5.0 mU/L carry significantly higher risk of miscarriage than those with lower TSH levels (<2.5 mU/L) [40]. Another study has similarly found that a rise in maternal TSH level may increase the risk of miscarriage. This risk becomes even greater at a TSH level >2.5 mU/L, accompanied by TPOAb positivity [41]. In one of several meta-analyses we reviewed, SCH during early pregnancy was associated with an increased risk of miscarriage, whether TSH level was >2.5 mU/L or exceeded the gestation-specific upper limit; and the miscarriage rate rose further if thyroid autoantibodies were present [42]. A second meta-analysis has indicated a higher risk of multiple adverse outcomes (eg, pregnancy loss, premature birth, and abruption) in the presence of SCH, and outcomes of the various studies were unchanged by substituting other TSH reference ranges [43].

In women receiving LT4 treatment for SCH, the risk of miscarriage in early pregnancy increases at a TSH level >4.5 mU/L. However, holding serum TSH to levels <2.5 mU/L seems to mitigate the risk [44], as do gradual LT4 dosage hikes (adjusted bi-weekly) in the course of pregnancy at serum TSH levels >2.5 mU/L [45]. A meta-analysis of nine studies has confirmed that LT4 use for SCH may effectively reduce the risk of pregnancy loss (RR = 0.19, CI: 0.08–0.39) and premature delivery (RR = 0.41, CI: 0.24–0.68) [46]. More evidence is still needed to fully assess the relation between LT4 therapy and outcomes of SCH, with or without TPOAb positivity.

Negro and colleagues have studied LT4 treatment in TPOAb-positive euthyroid patients, determined by TSH levels at first trimester (pretreatment mean, 1.6 ± 0.5 mU/L). LT4 dosing remained unchanged for the duration of pregnancy, given as follows: 0.5 μg/kg/day (TSH < 1.0 mU/L); 0.75 μg/kg/day (TSH 1.0–2.0 mU/L), or 1 μg/kg/day (TSH > 2.0 mU/L or TPOAb titer >1500 kIU/L) [47]. It was found that TPOAb-positive euthyroid pregnant women were associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with LT4 could decrease the risk of miscarriage and premature delivery. Nevertheless, Nazarpour et al. were able to lessen premature deliveries in a similar LT4 dosage for TPOAb-positive women with TSH levels ≥4 mU/L [48].

To date, two large randomized clinical trials of LT4 intervention in women experiencing SCH at weeks 13 or 17 of gestation have failed to show any improvement in the cognitive function of offspring. The Controlled Antenatal Thyroid Screening (CATS) study initiated LT4 screening and treatment (150 μg/day) for SCH and/or isolated hypothyroxinemia during gestation (mean, 13 weeks ± 3 days). There was no clear cognitive benefit to offspring at 3 years of age in the treated (vs. placebo) group [49]. Intelligence quotients (IQs) of offspring were again assessed at 9.5 years of age, with similar findings [50]. These negative results may be rooted in the following aspects: (1) late-onset intervention (i.e., 13 weeks of gestation), failing to capture initial bursts of rapid brain growth; (2) marginal degrees of SCH during pregnancy, TSH median values at 3.1 or 3.8 mU/L; (3) IQ testing of offspring and inordinately simplistic indices [51]; and (4) no individualized LT4 therapy. In certain instances, the starting dose (150 μg/day) may have been excessive. There was also a 10% rate of dose reductions due to biochemical or clinical signs of overtreatment [50]. Korevaar TI, et al. have found that high maternal FT4 concentrations during pregnancy may lower a child's IQ and negatively impact volumes of gray matter, as assessed by magnetic resonance imaging [52].

Another large multicenter RCT study conducted in the United States has since offset some shortcomings of the CATS trial. This second study enrolled women with SCH (mean TSH, 4.4–4.7 mU/L), evaluating offspring IQs at 5 years of age. The subjects were given different initial LT4 doses, and their thyroid function was monitored monthly to enable dosage adjustments. Once again, the outcomes were negative, perhaps due to later onset of LT4 intervention (~17 weeks of gestation) [53].

Results of a small prospective study have also demonstrated that in pregnant women with SCH at <7 weeks of gestation, LT4 treatment may truly protect mental [MDI] and physical [PDI] developmental indices [54]. In an animal study, the critical period of LT4 treatment appeared to be early pregnancy [55].

In summary, subclinical hypothyroidism may heighten risks of miscarriage, premature birth, and diminished IQ in offspring. LT4 intervention early in pregnancy is of potential benefit, helping to lower chances of miscarriage and improve offspring intellect. The presence of thyroid autoantibodies may additionally place women with TSH levels >2.5 mU/L at risk of miscarriage, which LT4 treatment perhaps mitigates. Although TPOAb-positive women with TSH levels <2.5 mU/L share an increased risk of miscarriage (OR = 2.71, 95% CI: 1.43–5.12) [41], the incidence seems unaffected by LT4 treatment.

In a prospective study, TPOAb-positive women (ages, 18–40 years) with early pregnancies and TSH levels of 0.5–2.5 mU/L received full-course LT4 intervention. Starting doses of LT4 were based on TSH levels, either 1 μg/kg/day (TSH 1.5–2.5 mU/L) or 0.5 μg/kg/day (TSH 0.5–1.5 mU/L), raising or lowering amounts by 0.5 μg/day at TSH levels >3 mU/L or <0.5 mU/L, respectively. The rates of miscarriage did not differ significantly when comparing TPOAb-positive (LT4-treated or untreated) and TPOAb-negative patients at the stated range of TSH (0.5–2.5 mU/L), nor were preterm delivery rates significantly different in LT4-treated and untreated patients [56]. Given these findings, LT4 intervention is not advocated in women with TSH levels <2.5 mU/L and TPOAb positivity. However, monitoring of thyroid function is still advised.

One critical question is whether LT4 treatment prior to conception will improve pregnancy outcomes in TPOAb-positive euthyroid women. This issue has been addressed by a multicenter, randomized, and placebo-controlled trial of once-daily LT4 (50 μg) given to TPOAb-positive euthyroid women (median TSH = 2.10 mU/L, IQR: 1.51–2.74). Subsequent rates of live births, pregnancy loss, or preterm birth and neonatal outcomes did not differ significantly in treated and untreated patient groups [57].

The relation between SCH in early pregnancy and adverse gestational outcomes or offspring performance remain controversial, but present therapeutic guidelines continue to support LT4 in this setting, given its safety. Nevertheless, available treatment options should be based on serum TSH level and TPOAb/TgAb positivity (Table 1) [1–3].

**Table 1** LT4 treatment options during pregnancy

| TSH (mU/L) | TPOAb/ TgAb | LT4 treatment |
|---|---|---|
| Above gestation-specific upper limit or >4.0 | +/− | Yes |
| Between 2.5 and gestation-specific upper limit or 4.0 | + | Yes |
| | − | No |
| Between gestation-specific lower limit or <0.1 and 2.5 | +/− | No |

*TSH* thyroid stimulating hormone, *TPOAb* thyroid peroxidase antibody, *TgAb* thyroglobulin antibody, *LT4* levothyroxine

## Initiation and optimization of therapeutic LT4 dosing to treat SCH in pregnancy

The various studies of initial LT4 dosing for subclinical hypothyroidism during pregnancy have produced disparate results. After administering daily 50 μg doses of LT4 for SCH during pregnancy, Cruz et al concluded that this regimen is insufficient to maintain normal thyroid function in most women (ie, serum TSH <4.5 mU/L or <3 mU/L) [58]. Verga and colleagues followed 185 pregnant women, 155 of them given LT4 prior to conception (subclinical hypothyroidism, 76; overt or postoperative hypothyroidism, 52). The other 30 (all SCH) received LT4 during gestation [35]. Maximum LT4 dosing needed to normalize serum TSH levels depended on the etiology of hypothyroidism. Final LT4 doses were cited as 101.0 (±24.6) μg daily for SCH, 136.8 (±30.4) μg daily for overt hypothyroidism, and 159.0 (±24.6) μg daily after surgical resection.

Our own researchers have noted that LT4 dosing is determined by baseline TSH levels in women with SCH. During early pregnancy, a daily dose of 50 μg typically applies at baseline TSH levels of 2.5–5.0 mU/L, whereas 75 μg is adequate at TSH levels of 5.1–8.0 mU/L, and 100 μg is reserved for TSH levels >8.0 mU/L. TSH may be reduced to ~1.0 mU/L after 4 weeks of treatment, thereby maintaining an optimal range of serum TSH in 79.3–90% of pregnant women [59]. The average LT4 starting dose used by Lazarus et al in the CATS study was 147 μg. Most women were started at 150 μg daily, with 85% continuing treatment at week 6. Only 10% required dose reductions (to 125 μg daily) due to declining TSH and rising FT4. A small percentage (5%) increased their daily dosages to 175 μg [49].

Marcos et al. examined 77 patients with newly diagnosed hypothyroidism during pregnancy, grouping them as SCH1a (TSH >2.5 mU/L [first trimester] or >3 [second or third trimester] but <4.2 mU/L); SCH1b (TSH > 4.21 but <10 mU/L); or OH. The target TSH level was <2.5 mU/L (in first trimester) or <3 mU/L (in second and third trimesters). The target doses of LT4 were plainly different. Those with SCH received lower doses of LT4 than those with OH (1.31 ± 0.36 vs. 2.33 ± 0.59 μg/kg/day); and dosing in the SCH1a group was significantly lower than in the SCH1b group (1.20 ± 0.39 vs. 1.42 ± 0.31 μg/kg/day). Final and initial doses were consistent in 89.06% of women with SCH and in 76.92% of women with OH. Only 11 and 23% of

patients, respectively required further dose adjustments. The time to reach normal thyroid function did not differ significantly by group [SCH, 3.3–6.06 weeks; OH, 1.8–5.3 weeks]. The initial dose of the SCH group was 84.85 ± 24.74 μg/day or 1.28 ± 0.36 μg/kg/day, compared with a final dose was 86.94 ± 25.21 μg/day or 1.31 ± 0.36 μg/kg/day. The initial dose of OH group was 133.44 ± 16.46 μg/day or 2.06 ± 0.46 μg/kg/day, compared with a final dose was 147.08 ± 29.83 μg/day or 2.33 ± 0.59 μg/kg/day [39].

## LT4 treatment for SCH after delivery

It must be emphasized that the increased demand for thyroid hormone during pregnancy in women with SCH (±TPOAb positivity) diagnosed prior to pregnancy is purely a gestational stipulation. Pre-pregnancy doses of LT4 should be resumed postpartum, and serum TSH should be reviewed at Week 6 after delivery. A follow-up study of 65 postpartum women with subclinical hypothyroidism (TSH > 3 mU/L) diagnosed during gestation (Week 28) took place during an average of 4.9 years. Thyroid function returned to normal in 49 (75.4%), but serum TSH level remained elevated (TSH > 4.5 mU/L) in 16 women (24.6%), only three of them treated with LT4. Patients positive for TPOAb are more likely to display TSH elevations and require LT4 treatment [60].

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.



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