REVIEW ARTICLE

Subclinical hypothyroidism in pregnancy: controversies on diagnosis and treatment

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KEY WORDS

diagnosis, pregnancy, subclinical hypothyroidism, treatment

ABSTRACT

The negative impact of even subtle maternal thyroid hormone deficiency on the pregnancy outcome and intellectual development of the progeny has been known for many years, but unfortunately the diagnosis and treatment of subclinical hypothyroidism in pregnant women still evokes controversies. Due to physiological changes in thyroid function and thyroid hormones metabolism during pregnancy, the trimester-specific reference ranges for thyroid-stimulating hormone (TSH) and free thyroid hormones should be established. However, because of interassay variability and other confounders including ethnicity and iodine intake, such norms are reliable only for local populations and a specific laboratory method. In turn, the fixed reference ranges suggested by endocrine societies may carry a risk of misclassificating some healthy pregnant women to be hypothyroid. The effect of levothyroxine treatment on pregnancy and children's cognitive outcomes remains unclear. Therapeutic benefits in decreasing miscarriage and preterm delivery rates were observed when intervention was held in the first trimester in women with a TSH level between 2.5 to 10 mU/l, mainly higher than or equal to 4 mU/l. The possible harmful effect of treatment includes preterm delivery, gestational diabetes, hypertension, and pre-eclampsia. The only 3 prospective, randomized, placebo-controlled trials evaluating the efficacy of levothyroxine therapy on children's intelligence quotient were started in the second trimester, which may be too late to demonstrate differences between treatment and placebo groups. Awaiting the results of future trials, clinicians should be aware of the fact that low-dose levothyroxine at a daily dose of 25 to 50 μg is probably not harmful and may be beneficial, but the routine implementation of the therapy in each pregnant women with a TSH level exceeding 2.5 mU/l seems too premature.

Introduction The significance of the effect of maternal thyroid hormone deficiency during pregnancy on child development was brought to endocrinologists' attention over 20 years ago. In 1999, Haddow et al[1] demonstrated that untreated overt hypothyroidism in pregnant women may adversely affect children's neurodevelopment. Although none of them had hypothyroidism as newborns, their intelligence quotient (IQ) scores assessed at the age of 7 to 9 years were 7 points lower and 19% of them had scores of 85 or lower compared with 5% of the matched control children. In the same year, Pop et al[2] reported that maternal free thyroxine (fT_4) concentration below the tenth percentile accompanied by the normal level of thyroid-stimulating hormone (TSH) at 12 weeks' gestation were associated with lower scores of development according to the Bayley Psychomotor Developmental Index in children at 10 months of age. The relative risk (RR) for impaired psychomotor development was 5.8 (95% CI, 1.3–12.6). Those results were confirmed in 2003 by the same team in children at the age of 1 and 2 years.[3] It also appeared that the negative impact of maternal early gestation hypothyroxinemia on infant neurodevelopment could be overcome when fT_4 concentration increased during the further course of pregnancy. From that time, a large body of literature on the adverse impact of maternal overt and subclinical hypothyroidism (SH) on obstetric and neonatal outcomes have been published. Numerous reports demonstrated that SH during pregnancy is associated with an increased risk of miscarriage, preterm delivery, placental abruption, gestational diabetes, hypertensive disorders of pregnancy, pre-eclampsia, intrauterine

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TABLE 1 Meta-analyses and observational studies documenting the association between maternal subclinical hypothyroidism during pregnancy and adverse obstetrical and neonatal outcomes

Study	Adverse outcome	OR (95% CI)	RR (95% CI)
Meta-analyses			
Liu et al[4]	Miscarriage	3.4 (1.62–7.15)	–
Toulis et al[5]	Gestational diabetes	1.39 (1.07–1.79)	–
Chan et al[6]	Pregnancy loss	1.93 (1.4–2.64)	–
	Preterm delivery	1.3 (1.05–1.6)	–
	Placental abruption	2.16 (1.15–4.06)	–
	Breech presentation at term	2.3 (1.5–3.51)	–
Maraka et al[7]	Miscarriage/pregnancy loss	–	2.01 (1.66–2.44)
	Preterm delivery	–	1.2 (0.97–1.5)
	Placental abruption	–	2.14 (1.23–3.7)
	Growth restriction	–	1.7 (0.83–3.5)
	Pre-eclampsia	–	1.3 (1–1.68)
	Gestational diabetes	–	1.28 (0.9–1.81)
	Neonatal death	–	2.58 (1.41–4.73)
Tong et al[8]	Growth restriction	1.54 (1.06–2.25)	–
Gong et al[9]	Gestational diabetes	1.56 (1.29–1.88)	–
Van den Boogaard et al[10]	Pre-eclampsia	1.7 (1.1–2.64)	–
Zhang et al[11]	Miscarriage/pregnancy loss	1.9 (1.59–2.27)	–
Observational studies			
Karakosta et al[12]	Growth restriction	3.1 (1.22–8.01)	–
	Gestational diabetes	4.33 (2.1–8.91)	–
Chen et al[13]	Pre-eclampsia	2.24 (1.25–4.02)	–
	Growth restriction	3.36 (1.75–6.38)	–
Ying et al[14]	Gestational diabetes	1.81 (1.08–1.73)	–
Arbib et al[15]	Preterm delivery	1.81 (1.02–3.28)	–
Vrijkotte et al[16]	Large for gestational age in males	1.95 (1.22–3.11)	–
Carty et al[17]	Lower birth weight	–	–
Furukawa et al[18]	Gestational diabetes	–	–
Yang et al[19]	Preterm delivery	4.58 (1.46–14.4)	–
Kianpour et al[20]	Miscarriage	–	5.93 (1.711–20.62)
Wu et al[21]	Hypertensive disorders	4.04 (1.85–8.84)	–
Zhang et al[22]	Miscarriage	3.53 (1.85–6.75)	–
	Maternal composite outcomes	2.19 (1.26–3.81)	–

Abbreviations: OR, odds ratio; RR, relative risk

growth restriction, large for gestational age, and low birth weights (TABLE 1).[4-22] However, in several studies, no adverse perinatal outcomes of SH were found.[23-26] Those inconsistent findings may be related to different criteria used for the diagnosis of SH, coexistence of antithyroid antibodies, which are considered an independent risk factor for adverse pregnancy outcomes, discrepant maternal age of the studied groups, and various gestational age of thyroid function evaluation. A similar inconsistency can be observed in terms of the relation among maternal SH during pregnancy and neurodevelopmental disorders in children such as lower intelligence scores, autism, and attention-deficit hyperactivity disorder (ADHD). A 2018 meta-analysis involving 11 studies published between 1999 and 2015 demonstrated a significant relationship between maternal SH during the first half of pregnancy and intellectual disability in early childhood. The odds ratio (OR) of the cognitive developmental disorder risk was 2.14 (95% CI, 1.2–3.83; $P = 0.01$).[27] Poorer neurodevelopment including lower IQ and motor scores, impaired vision development, and decrement in the general cognitive index were noted at 6 and 25 to 30 months of age and later at 5 to 8 years of age. Williams et al[28] demonstrated in children at 5.5 years of age a 3.2-point decrement in the general cognitive index for each milliliter per liter increment in maternal TSH.[28] However, in several studies, no link between maternal SH and offspring's intellectual deficits assessed at 6, 12, 24, 36, and 60 months of age was noted.[29-32] In the same 2018 meta-analysis, no association between maternal SH and autism and ADHD in children was found based on 3 and 5

studies, respectively.[27] However, in the recent case-cohort study by Andersen et al,[33] an increased risk of autism spectrum disorder was observed with a hazard ratio (HR) of 1.7 (95% CI, 1.04–2.75), but no relation was found between maternal SH and ADHD and epilepsy.[33] In view of this evidence, there is a strong suggestion that maternal SH during pregnancy has a deleterious impact on obstetric outcomes and children's neurodevelopment. Unfortunately, numerous uncertainties concerning the diagnosis and treatment of SH have arisen.

How to recognize subclinical hypothyroidism in pregnancy Pregnancy profoundly changes thyroid function and thyroid hormones metabolism. Therefore, reference ranges for thyroid function tests (TFTs) in pregnant women differ from those in the nonpregnant population and among trimesters. Placental human chorionic gonadotropin (HCG), which exhibits structural similarity to TSH and contains 1/4000 thyrotropic activity of TSH, stimulates the thyroid gland directly through the TSH receptor. It reaches the highest level at about 10 weeks' gestation, and decreases to a plateau in the second and third trimesters. There is an inverse relationship between HCG and TSH throughout pregnancy: the peak concentration of HCG in first trimester corresponds with the reduction of TSH secretion, then TSH slightly rises during the second and third trimesters, but it does not reach the prepregnancy values. Therefore, the upper and lower TSH normal limits decrease, change by trimester, and TSH secretion can be transiently suppressed. As a consequence of HCG stimulation, serum concentrations of fT_4 and free triiodothyronine (fT_3) increase during the first trimester, but in the further course of pregnancy its values decrease because of transplacental transfer to the fetus, degradation by placental type 3 iodothyronine deiodinase, and increased renal filtration.

The range of normal serum total T_4 (TT_4) and T_3 (TT_3) concentrations during pregnancy is greater because of a rapid increase in thyroxine-binding globulin (TBG) levels. Therefore, in the second and third trimesters, the nonpregnant TT_4 and TT_3 range should be multiplied 1.5-fold.

Subclinical hypothyroidism is defined as the presence of elevated serum TSH levels with normal fT_4 or TT_4 values, but determining the upper normal TSH limit in the pregnant population remains challenging. There is a general agreement among the international and Polish recommendations concerning the diagnosis and management of thyroid disease during pregnancy. The most valid reference ranges for the levels of TSH and thyroid hormones are those established by medical centers for a local population of healthy, iodine-sufficient, thyroid peroxidase antibody (TPOAb)–negative pregnant women without thyroid disease.[34-36] Implementing these recommendations may be difficult, because TSH and, to some extent, fT_4 levels do not follow a Gaussian distribution and are skewed toward upper values, so that a minimum of 400 individual measurements is required to set reference intervals.[37]

Another limitation of such population-derived reference ranges is that they are assay-specific. Springer et al[38] demonstrated that TSH reference ranges established simultaneously with 7 different analytical systems representing immunoassays most often used worldwide in 229 women in early pregnancy may vary between 0.18 to 2.78 mU/l and 0.25 to 3.9 mU/l. McNeil and Stanford[39] documented in their elegant review that trimester-specific TSH 97.5 percentiles differed among the assays used and fell into 2 groups: according to Architect, Beckman, and Immulite assays, first trimester TSH 97.5 percentiles were around 3 mU/l, and according to Centaur and Roche assays, they were closer to 4 mU/l. Only 4 out of 27 studies reported this value to be close to 2.5 mU/l. However, other authors did not confirm relevant interassay differences for TSH, but pointed out a large interassay dependance of fT_4 measurements: up to 100% of fT_4 levels determined by a single immunoassay as normal were outside the reference range established by another immunoassay.[40] It means that patient results obtained by a particular analytical method should be referred to the reference ranges obtained with the use of the same assay, otherwise a serious misclassification may occur.

Trimester- and assay-specific reference intervals for TSH levels should not be uncritically extrapolated from one population to another. In several studies, differences in serum TSH levels among pregnant women from different ethnic groups have been shown. In 2 American and 2 European studies, a lower median TSH level was found in black pregnant women compared with the white ones: 1.1 vs 1.5 mU/l, 0.82 vs 1.02 mU/l, 1.3 vs 1.5 mU/l, and 0.77 vs 1.12 mU/l.[41-44] In turn, Asian women had the highest TSH concentrations.

In the 2 studies from the Netherlands,[45,46] the higher mean TSH values were found in Dutch women compared with Moroccan and Surinamese women: 1.5 vs 1.29 and 1.33 mU/l, respectively, according to Korevaar et al.[45] As suggested by Peters et al,[47] those differences may be due to the distinct thyroid–pituitary axis setpoints among people of various ethnic backgrounds and also in different HCG levels.[47]

Iodine dietary supply, an essential substrate for thyroid hormone synthesis, is another crucial factor that influences TFTs. Iodine requirement in pregnancy increases by 50% concurrently with 50% increase in thyroid hormone synthesis: from 150 μg in the nonpregnant adult population to 250 μg daily in the pregnant one. According to the World Health Organization recommendations, the urinary iodine concentration (UIC) of 150 to 249 μg/l is a good indicator of an adequate iodine intake in pregnant populations yet not in individual patients. Some studies, but not all, reported that iodine deficiency

TABLE 2 Population-derived, trimester-specific reference ranges for thyroid-stimulating hormone, free thyroxine, and free triiodothyronine established for the Polish population using the electrochemiluminescence method (Elecsys, Roche) (data for pregnant women from Kostecka-Matyja et al[62])

Thyroid function test parameter	General population	Pregnant women		
		First trimester	Second trimester	Third trimester
TSH, mU/l	0.3–4.5	0.009–3.177	0.05–3.442	0.11–3.53
fT_3, pmol/l	3.1–6.8	3.63–6.55	3.29–5.45	3.1–5.37
fT_4, pmol/l	11–22	11.99–21.89	10.46–16.67	8.96–17.23

Abbreviations: fT_3, free triiodothyronine; fT_4, free thyroxine; TSH, thyroid-stimulating hormone

TABLE 3 Thyroid-stimulating hormone upper limit and thyroid-stimulating hormone reference ranges for each trimester of pregnancy established arbitrarily by Polish and international endocrine societies

Author of recommendation	TSH, mU/l		
	First trimester	Second trimester	Third trimester
Polish Society of Endocrinology, 2011[34]	–2.5	–2.5	–2.5
American Thyroid Association, 2011[56]	0.1–2.5	0.2–3	0.3–3
Endocrine Society, 2012[57]	–2.5	–3	–3.5
European Thyroid Association, 2014[35]	–2.5	–3	–3
American Thyroid Association, 2017[36]	–4	–4	–4

Abbreviations: see TABLE 2

strongly increases TSH levels in pregnancy.[48] However, elevated (UIC >250–499 μg/l) and excessive (UIC >500 μg/l) iodine intake can also exert a deleterious effect on thyroid function, which results in an increase of TSH and decrease of fT_4 concentrations and a higher prevalence of SH.[48,49]

Different TFT results can also be observed in multiple pregnancies, commonly accompanied by higher HCG and lower TSH levels.[50,51] For this reason, women with multiple pregnancy should be excluded from reference populations.

The body mass index (BMI) may constitute another factor influencing TFT results in pregnancy. Several observations documented higher TSH and lower fT_4 concentrations in pregnant women with a BMI greater than 25 to 30 kg/m^2.[51-53]

Cigarette smoking, although might induce changes in TFTs in the nonpregnant population, has a rather limited influence on mean TSH concentrations in pregnancy.[54-57] However, some changes in thyroid hormones concentration in smokers compared with nonsmokers were observed.[55,58,59]

Age might be another confounding factor influencing TSH levels, as those may increase with age.[58,60] According to the Pearce et al,[58] in pregnant women, TSH levels increased by 0.03 mU/l for every year of maternal age (P = 0.03).

As demonstrated by Bestwick et al,[61] issues related to interassay, ethnic, and maternal weight differences in TSH and fT_4 levels can be overcome by using the multiple of the median (MoM). The MoM value is calculated by dividing each individual result by the population median value and is a measure of how far an individual test result deviates from the median value for a particular population. For instance, Bestwick et al[61] calculated an increase in TSH levels of 0.025 MoMs and a decrease in fT_4 levels of 0.009 MoMs per a 10-kg increase in body weight.

The trimester-specific reference ranges of TSH and free thyroid hormones levels for the Polish population, assessed by the electrochemiluminescence method, were established in a multicenter study[62] and presented in TABLE 2.

When local population-derived, trimester-, and assay-specific reference ranges for TSH are not available, the authors of 2017 American Thyroid Association (ATA) guidelines advise clinicians to use the reference ranges obtained from similar patient populations.[36] If such norms are inaccessible, Polish and international endocrine societies recommend the use of fixed reference intervals based on published studies (TABLE 3). According to 2011 ATA, 2012 Endocrine Society, and 2014 European Thyroid Association (ETA) guidelines, the upper normal limit for TSH is quite similar: 2.5 mU/l for the first, 3 mU/l for the second, and 3 to 3.5 mU/l for the third trimester.[35,63,64] In 2017, the ATA issued new guidelines with fixed TSH reference intervals up to 4 mU/l for each trimester of pregnancy.[36] These new cutoffs were derived based on the recent data from India, China, Korea, the Unites States, and the Netherland, which showed only a modest TSH level reduction in the first-trimester upper reference limit of 0.5 to 1 mU/l at weeks 7 to 12. Interestingly, a similar observation was made by the Danish authors.[65] Analyzing TSH and fT_4 setpoints in pregnant women, the authors of the 2017 ATA recommendations stated that a significant fT_4 reduction had occurred only when the serum TSH level was higher than 4.8 mU/l.

The use of previously recommended fixed TSH upper-limit cutoffs of 2.5 to 3 mU/l could lead to misclassification of some healthy pregnant women as having SH. According to Medici et al,[66] 8.6% and 4.9% of healthy, TPOAb-negative pregnant women with TSH levels within the population-derived reference range had TSH values above 2.5 and 3 mU/l in the first and second trimester, respectively.[66] An even higher rate of misclassification was reported by Li et al[67]: 27.8% of Chinese pregnant women in the first trimester had TSH levels above 2.5 mU/l, whereas only 4% of them had TSH levels above the upper limit of population-based reference intervals.

A varying criterion for establishing the upper normal limit of TSH levels have also influenced the reported prevalence of SH in pregnancy: from 1.5% to 42.9% according to a 2018 meta-analysis of 56 studies.[68] After pooling samples, the SH prevalence was 3.47% among studies using population-derived 97.5-percentile TSH cutoff,

14.39% when the 2011 ATA TSH cutoffs were used, and 4.05% when the 2017 ATA TSH cutoffs were adopted.

The estimation of fT_4 serum concentrations in pregnancy poses even a greater challenge than in the case of TSH. The commonly used indirect commercial tests strongly depend on serum-binding proteins including thyroxine-binding globulin and albumins and also on free fatty acids. Thyroxine--binding globulin and free fatty acid levels typically rise during pregnancy, while albumins decrease. Consequently, those tests can provide falsely high or falsely low results. Similarly to TSH results, fT_4 measurements exhibit interassay differences and may be influenced by ethnic features, maternal weight, age, and smoking habits: lower fT_4 levels were observed in pregnant women with increasing BMI and age and among smokers.[55,58,59]

Nowadays, the reference method that is free of commercial test limitations is the measurement of the levels of free thyroid hormones in dialysate or ultrafiltrate using solid-phase extraction with liquid chromatography / tandem mass spectrometry.[63] However, this reference method is still unavailable in everyday clinical practice. The suggested alternative strategy to fT_4 determination is to measure TT_4 concentration and use the nonpregnant reference ranges (5–12 μg/dl or 50–150 nmol/l) multiplied 1.5-fold or to calculate the fT_4 index. The latter 2 methods are rarely used in European countries.

Can levothyroxine therapy prevent the adverse effect of subclinical hypothyroidism on pregnancy and neonatal outcomes? **Evidence for treatment benefits related to pregnancy outcomes** Although there has been a large body of data on the negative impact of SH on pregnancy outcomes, evidence on levothyroxine ($L\text{-}T_4$) therapy benefits in reducing pregnancy complications remains unclear. In 2010, in a prospective interventional trial, Negro et al[69] evaluated the impact of $L\text{-}T_4$ therapy on TPOAb--positive pregnant women with TSH levels exceeding 2.5 mU/l. The intervention was performed in the first trimester and the $L\text{-}T_4$ dose was titrated to maintain a TSH level below 2.5 mU/l in the first trimester and below 3 mU/l in the second and third trimesters. Levothyroxine therapy resulted in a significant decrease in a composite of adverse pregnancy outcomes.[69] In 2017, Nazarpour et al[70] assessed the results of $L\text{-}T_4$ treatment in TPOAb-positive pregnant women without overt thyroid dysfunction. The dose of $L\text{-}T_4$ in the intervention group was TSH-dependent: 0.5 μg/kg daily for a TSH level below 1 mU/l, 0.75 μg/kg daily for a TSH level of 1 to 2 mU/l, and 1 μg/kg daily for a TSH level above 2 mU/l or a TPOAb titer above 1500 IU/ml; dosage was maintained throughout gestation. In that small, prospective, randomized study including 65 treated and 66 untreated individuals, the authors demonstrated that $L\text{-}T_4$ therapy was beneficial in reducing the incidence of preterm delivery (RR, 0.3; 95% CI, 0.1–0.85; $P = 0.0229$) and newborn admissions to the neonatal unit (RR, 0.17; 95% CI, 0.04–0.73; $P = 0.005$), but that effect was mainly observed in women with a TSH level higher than or equal to 4 mU/l.[70] As TPOAb-positivity may be an independent confounder of the obtained results, in 2018, the same team presented the effect of $L\text{-}T_4$ intervention in 366 pregnant women with SH who were TPOAb-negative. Subclinical hypothyroidism was defined as TSH levels ranging between 2.5 to 10 mU/l. Levothyroxine treatment was initiated in the first trimester and resulted in a significant reduction in the rate of preterm delivery in the group of women with TSH levels higher than or equal to 4 mU/l (RR, 0.38; 95% CI, 0.15–0.98; $P = 0.04$) yet not in those with a TSH level of 2.5 to 4 mU/l.[71] In a Chinese prospective study of Zhao et al[72] conducted in 93 women with SH (TSH level >2.5 mU/l in the first trimester; TSH level >3 mU/l in the second trimester), patients were randomized to 3 groups: treated at 8 to 10 weeks' gestation, treated at 13 to 16 weeks' gestation, and untreated. The target TSH level during $L\text{-}T_4$ therapy was lower than or equal to 3 mU/l. A significant reduction in the rate of overall pregnancy complications including gestational hypertension, pre-eclampsia, gestational diabetes, and anemia was found in women treated with $L\text{-}T_4$ at 8 to 10 weeks' gestation compared with those treated at 13 to 16 weeks' gestation and those untreated: 9.7% vs 41.9% vs 64.5%; $P < 0.01$. When stratified by the TPOAb status, $L\text{-}T_4$ therapy reduced pregnancy complications in women who were TPOAb-positive, even when the treatment was started in the second trimester.[72] However, no benefits of treatment were reported in 2 other trials. A study by Casey et al[73] assessed the effect of $L\text{-}T_4$ in 677 women with SH and 526 women with isolated hypothyroxinemia at a mean of 16.7 weeks' gestation. The reference ranges for gestational TFTs were population-derived: the TSH cutoff for SH was higher than or equal to 4 mU/l, and the fT_4 cut-off for hypothyroxinemia was below 0.8 ng/dl. The initial dose of $L\text{-}T_4$ in women with SH was 100 μg daily, and then the dose was adjusted to achieve the target TSH level of 0.1 to 2.5 mU/l. The effect of $L\text{-}T_4$ intervention was similar to that of placebo in preventing pregnancy complications such as miscarriage, preterm delivery, pre-eclampsia, gestational diabetes, and a composite neonatal outcome.[73] Another randomized, placebo-controlled multicenter TABLET (Thyroid Antibodies and Levothyroxine Trial) study, was designed to assess whether the use of $L\text{-}T_4$ would increase the rates of live births among euthyroid women with TPOAb. A total of 952 participants were recruited among women with a history of at least a single miscarriage or infertility. Euthyroidism was defined as a TSH serum concentration of 0.44 to 3.63 mU/l, which covered the second and third quartiles of the 3 assays used. Treatment with 50 μg of $L\text{-}T_4$ daily was initiated in the preconception period and continued throughout the pregnancy. There were no differences between the treatment and placebo groups

TABLE 4 Effects of levothyroxine treatment for subclinical hypothyroidism on pregnancy outcomes

Study	Design	Definition of subclinical hypothyroidism	Time of intervention	Treatment outcome	Comments
Negro et al[69]	Prospective, randomized	TSH >2.5 mU/l and normal fT_4	First trimester	Decrease in the composite of adverse pregnancy outcomes	Population positive for TPOAb
Nazarpour et al[70]	Prospective, randomized	TSH of 2.5–10 mU/l and normal fT_4I of 1–4.5	First trimester	Decrease in the incidence of preterm deliveries and newborn admissions to the neonatal unit	Population positive for TPOAb; a beneficial effect of treatment only when TSH ≥4 mU/l yet not in patients with TSH of 2.5 to <4 mU/l
Casey et al[73]	Prospective, randomized, placebo--controlled	TSH ≥4 mU/l and normal fT_4 at 11–24 pmol/l	Mean, 16.7 weeks' gestation	No beneficial effects of treatment on pregnancy and neonatal outcomes	TPOAb status uncertain
Maraka et al[75]	Retrospective	TSH of 2.5–10 mU/l	Uncertain	Decrease in the rate of pregnancy loss	TPOAb status uncertain; a beneficial effect of treatment only when TSH at 4.1–10 mU/l yet not in patients with TSH of 2.5–4 mU/l; increased incidence of preterm delivery, gestational diabetes, gestational hypertension and pre-eclampsia
Nazarpour et al[71]	Prospective, randomized	TSH of 2.5–10 mU/l and normal fT_4I at 1–4.5	First trimester	Decrease in the rate of preterm delivery	Population negative for TPOAb; a beneficial effect of treatment only when TSH ≥4 mU/l yet not in patients with TSH of 2.5 to <4 mU/l
Zhao et al[72]	Prospective, randomized	TSH >2.5 mU/l in the first trimester, >3 mU/l in the second trimester	First or second trimester	Reduction of overall pregnancy complications including gestational hypertension, pre--eclampsia, anemia, gestational diabetes	Population positive for TPOAb in 32%; a beneficial effect in women with TSH >2.5 mU/l treated at 8–10 weeks' gestation compared with those treated at 13–16 weeks' gestation or untreated; no conclusion on the rate of pregnancy loss
Dhillon-Smith et al[74]	Prospective, randomized, double-blind, placebo--controlled	TSH >2.5–3.6 mU/l	Preconception period	No beneficial effect of treatment on the rate of live birth, pregnancy loss, preterm delivery, or neonatal outcomes	Population positive for TPOAb
Zhang et al[22]	Retrospective	TSH of 2.5–10 mU/l, normal fT_4	First trimester	Reduction in the incidence of miscarriage	Population positive for TPOAb in 27.4%; a beneficial effect of treatment also when TSH at 2.5–4.8 mU/l but an increased risk of gestational diabetes

Abbreviations: fT_4I, free thyroxine index; TPOAb, thyroid peroxidase antibody; others, see TABLE 2

in terms of live-birth rates: 37.4% vs 37.9% (RR, 0.97; 95% CI, 0.83–1.14; $P = 0.74$) or in the other pregnancy outcomes including pregnancy loss or preterm birth, or in neonatal outcomes. Although the study was mainly addressed to the euthyroid, TPOAb-positive women, an additional analysis was performed in subgroups with TSH levels lower than or equal to 2.5 mU/l and exceeding 2.5 mU/l and no differences were noted between intervention and placebo groups regarding primary and secondary outcomes.[74]

In another study, Maraka et al [75] analyzed both benefits and adverse effects associated with L-T_4 therapy for SH. In that retrospective cohort study of 5405 pregnant women with a TSH level of 2.5 to 10 mU/l and an uncertain TPOAb status, L-T_4 therapy significantly diminished the incidence of pregnancy loss by 38% (P <0.01), but increased some pregnancy complications including preterm delivery (OR, 1.6; 95% CI, 1.14–2.24), gestational diabetes (OR, 1.37; 95% CI, 1.05–1.79), and pre--eclampsia (OR, 1.61; 95% CI, 1.1–2.37). The favorable effect of L-T_4 treatment was observed only in pregnant women with a TSH level of 4.1 to 10 mU/l yet not in those with a TSH level of 2.5 to 4 mU/l. Moreover, in women with a TSH level of 2.5 to 4 mU/l, L-T_4 treatment posed an increased risk of gestational hypertension compared with untreated patients with TSH within the same range (OR, 1.76; 95% CI, 1.13–2.74). No significant interaction was found between the pretreatment TSH concentration and adverse effect of thyroid hormone use on any other pregnancy outcome.[75] In a similar retrospective study evaluating the data of 3296 Chinese pregnant women, Zhang et al[22] reported that L-T_4 treatment administered in a subgroup of 266 individuals decreased the risk of miscarriage among women

with a TSH level of 2.5 to 4.08 mU/l (27.4% of them were TPOAb-positive) (OR, 0.05; 95% CI, 0.01–0.35) and in the group of women with a TSH level of 4.08 to 10 mU/l (34.2% of them were TPOAb-positive) by 23% (P <0.001), but it doubled the risk of gestational diabetes in the group with a TSH level of 2.5 to 4.08 mU/l (OR, 1.8; 95% CI, 1.2–2.69).[22]

It is difficult to draw firm conclusions based on the results of the presented 8 studies (TABLE 4) owing to different definitions of abnormal TSH levels (>2.5 mU/l, ≥4 mU/l, and 2.5–10 mU/l), varying TPOAb status (positive, partly positive, negative, and uncertain), time of treatment intervention (first trimester, second trimester, and uncertain), and various target TSH levels (0.1–2.5 mU/l, <2.5 mU/l, and ≤3 mU/l). Despite these discrepancies, it should be emphasized that in 6 out of 8 trials the positive effects of L-T_4 treatment, mainly in reducing the rate of pregnancy loss, were observed. In 5 studies that demonstrated the benefits of treatment L-T_4 was administered in the first trimester. The importance of early intervention was stressed by Zhao et al,[72] who observed better results when the treatment was started at 8 to 10 weeks' gestation compared with 13 to 16 weeks' gestation. However, in the TABLET study, which did not demonstrate L-T_4–related benefits, the intervention was initiated before conception.

In 5 out of 6 studies in which a favorable effect of L-T_4 treatment was found, the study population was TPOAb- positive, and only a single study reported treatment benefits in TPOAb-negative women yet exclusively in those with a TSH level higher than or equal to 4 mU/l and not in those with a TSH level of 2.5 to 4 mU/l. This raises doubts as to whether the implementation of therapy in pregnant women with a TSH level ranging from 2.5 mU/l to the upper normal limit who are TPOAb-negative might be beneficial and further research in this group of women is needed.

The most intriguing issue concerning SH in pregnancy is the TSH level at which a medical intervention should be performed. Based on the presented studies, it remains unresolved primarily because of the varying TPOAb status, which carries an additional risk of pregnancy loss.

Unexpectedly, in 2 studies,[22,75] the adverse effects of L-T_4 therapy were documented. However, in their small prospective study, Zhao et al[72] observed the beneficial effect of L-T_4 therapy in women with a TSH level above 2.5 mU/l in decreasing the rate of pregnancy complications. Further studies on potential L-T_4 therapy side effects in pregnant women are essential.

Evidence for the beneficial treatment effect on children's cognitive outcomes There were 3 prospective, randomized, controlled trials assessing the influence of L-T_4 therapy for maternal SH on children's IQ. The CATS (Controlled Antenatal Thyroid Screening) study randomized 880 pregnant women with TSH levels exceeding 97.5 percentile (subclinical hypothyroidism) or fT_4 levels lower than 25 percentile (isolated hypothyroxinemia), or both to L-T_4 treatment or placebo. The intervention was performed at a median gestational age of 13 weeks and 3 days with an initial L-T_4 dose of 150 μg per day. Then, the treatment was adjusted as needed to gain a target TSH level of 0.1 to 1 mU/l. In 10% of participants, the initial L-T_4 dose of 150 μg was lowered because of overdosage. Children's cognitive function was assessed at 3 years of age and no difference was found between those whose mothers were treated (mean IQ score, 99.2) or untreated (mean IQ score, 100) during pregnancy (P = 0.4). The percentage of children with an IQ score lower than 85 was 12.1% in the treated group and 14.1% in the control group (P = 0.39).[76] Similar results were obtained in the CATS II study that measured IQ in the same group of children at the age of 9.5 years. It included 119 children of treated mothers, 98 of those untreated, and 232 of those with normal gestational TFT results. Interestingly, there was also no difference in IQ below 85 between children of mothers with normal and subnormal gestational TFT results (OR, 1.15; 95% CI, 0.52–2.51; P = 0.73). Another relevant observation coming from that trial was that the oversupplementation of L-T_4 resulting in an fT_4 level exceeding 97.5 percentile had no detrimental effect on the percentage of children with an IQ score below 85, but it significantly increased the incidence of ADHD symptoms and behavioral difficulties.[77] In the aforementioned study of Casey et al,[73] in which the effect of L-T_4 in 677 women with subclinical hypothyroidism and 526 women with hypothyroxinemia at a mean time of 16.7 weeks' gestation was assessed, children's IQ score at 5 years of age constituted the primary outcome. The authors found no difference in terms of children's IQ between L-T_4 and placebo groups. The median IQ score of children of mothers with SH was 97 (95% CI, 94–99) in the L-T_4 group and 94 (95% CI, 92–96) in the placebo group (P = 0.71).[66]

The CATS study and the trial of Casey et al[73] were criticized because of the late time of treatment initiation. In fact, in both trials, the intervention with L-T_4 was started and target TSH levels were achieved in the second trimester of pregnancy, after the main steps of organogenesis were completed. Of note, there is a warning against the oversupplementation of L-T_4 coming from the study of Korevaar et al.[78] The authors observed that both low (below 12.2 pmol/l) and high (above 20.1 pmol/l) maternal fT_4 concentrations during early pregnancy (<18 weeks) were associated with lower child's IQ and lower grey matter and cortex volume on magnetic resonance imaging at 6 to 8 years of age.[78]

Recommendations for the management of subclinical hypothyroidism in pregnancy In the face of the inconsistent results of L-T_4 treatment for SH in pregnancy, the recommendations issued by national and international endocrine societies

vary. The Polish Society of Endocrinology (PSE) in the guidelines issued in 2011 recommends clinicians to treat women in the preconception period when TSH levels are above 2 to 2.5 mU/l, especially in the case of TPOAb positivity, and to treat all women with SH recognized during pregnancy (fixed TSH upper limit, 2.5 mU/l for each trimester) irrespective of TPOAb status.[34] The adopted TSH cutoff of 2.5 mU/l in the preconception period was mainly based on reference intervals established by the American National Academy of Biochemical Chemistry in the population of euthyroid, healthy volunteers free from detectable TPOAbs or thyroglobulin antibodies and any personal or family history of thyroid dysfunction yet not based on a Polish population survey.[79]

Similarly, in 2014, the ETA issued a recommendation to treat SH in all women before conception and during pregnancy and to keep TSH values within the trimester-specific pregnancy reference range.[35] Of note, the ETA arbitrarily established upper normal limit for TSH was higher in the second and third trimester than that proposed by PSE (3 and 3.5 mU/l vs 2.5 and 2.5 mU/l, respectively).

The latest 2017 ATA guidelines take into account both TSH level and TPOAb status assuming that there is a synergistic negative effect of TPOAb and thyroid hormone deficiency on the pregnancy outcome. The ATA strongly recommends L-T_4 treatment in TPOAb-positive women with a TSH level above the pregnancy-specific upper normal range and suggests considering treatment initiation in TPOAb-positive women with a TSH level between 2.5 mU/l and the upper normal limit. In TPOAb-negative women, the treatment is recommended when a TSH level is higher than or equal to 10 mU/l and advised to be considered when a TSH level is above the normal limit and below 10 mU/l. Pregnant women who are TPOAb-negative and have TSH levels between 2.5 mU/l and the upper normal limit do not need treatment. The ATA arbitrarily proposed upper normal limit for TSH levels for each trimester of pregnancy is 4 mU/l, and the target TSH level during L-T_4 treatment is below 2.5 mU/l, which is quite different from PSE and ETA proposals.[36] Although the ATA guidelines do not define the normal TSH range in the preconception period, according to the American National Health and Nutrition Examination Survey III, the normal TSH reference intervals for the healthy reference population negative for thyroid antibodies and not taking androgens or estrogens is 0.47 to 4.15 mU/l.[80]

The statement of the American Congress of Obstetricians and Gynecologists published in 2015 is in sharp contrast to the recommendations issued by endocrinology societies, as it assumes that currently there is no evidence showing that the identification and treatment of SH during pregnancy improves the outcomes.[81] On the contrary, the guidelines issued in 2015 by the Practice Committee of American Society for Reproductive Medicine state that the treatment of SH defined as a TSH level exceeding 4 mU/l is associated with improved pregnancy outcomes and lower miscarriage rates, but insufficient evidence exists for treatment benefits in women with a TSH level of 2.5 to 4 mU/l.[82]

Summary and authors' opinion It should be emphasized that several new trials have been published from the time the last guidelines were released and next ones are ongoing, which makes the flow of information quite dynamic. To summarize the previous and recent data concerning SH in pregnancy, it can be assumed that:

- Pregnancy-specific population-derived reference ranges of TSH and fT_4 levels for each trimester are needed to avoid a false-positive diagnosis and unnecessary treatment.
- In view of the lack of such norms, considering Polish observations, the TSH upper limit for the general population should be diminished by 1 to 1.5 mU/l in the first trimester and by 0.5 to 1 mU/l in the second and third trimesters.
- Levothyroxine treatment introduced in the first trimester can prevent the pregnancy loss, but it may increase the rate of some pregnancy complications including preterm delivery, gestational diabetes, gestational hypertension and pre-eclampsia.
- The most beneficial treatment effect is probably achieved in women with a TSH level higher than or equal to 4 mU/l and the effect is uncertain in the case of a TSH level ranging from 2.5 to less than 4 mU/l, especially when the patient tested negative for TPOAb.
- Due to the potential negative impact of L-T_4 treatment on the mother's and child's health, which should be further explored, a precaution regarding L-T_4 overdosage should be made and strict surveillance of maternal status and regular glucose measurements, for instance every 2 months, are advised.
- The implementation of L-T_4 treatment in the second trimester does not improve the intellectual development of the progeny.
- New trials assessing the effect of L-T_4 treatment started early in the first trimester on children's IQ are needed.

The great area of uncertainty still remains and concerns the following issues:

- Do pregnant TPOAb-negative women with a TSH level between 2.5 and less than 4 mU/l benefit from L-T_4 treatment?
- What is the target TSH level during L-T_4 treatment in pregnant women: lower than or equal to 2.5 mU/l or below the trimester-specific upper limits?
- Should not only the TSH but also fT_4 level be a relevant target of therapy, especially in the first trimester, to avoid the negative effect of both low and high fT_4 values?
- Is TPOAb positivity or previous pregnancy loss an indication to start L-T_4 therapy at lower TSH levels of 2.5 to 4 mU/l?

Our review was intended to point out the controversies in the diagnosis and treatment of SH in pregnant women. However, a clinician would rather prefer to get strict recommendations. Also, the management of SH in infertile women undergoing in vitro fertilization and women with isolated gestational hypothyroxinemia, although very important, is beyond the scope of this review.

Awaiting the results coming from future trials, a clinician should be aware of the fact that, in difficult clinical scenarios, the implementation of low-dose L-T_4 at 25–50 μg daily is probably not harmful and may be beneficial, but high fT_4 levels might have a negative impact on the pregnancy outcome and children's IQ and behavior.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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