Subclinical hypothyroidism in pregnancy: controversies on diagnosis and treatment

Authors: Małgorzata Gietka-Czernel, Piotr Glinicki

Article type: Review article

Received: July 15, 2020.

Accepted: September 20, 2020.

Published online: September 25, 2020.

ISSN: 1897-9483
Subclinical hypothyroidism in pregnancy: controversies on diagnosis and treatment

Małgorzata Gietka-Czernel, Piotr Glinicki

Department of Endocrinology, Centre of Postgraduate Medical Education, Warsaw, Poland.

Short title: Subclinical hypothyroidism in pregnancy.

Corresponding author:

Piotr Glinicki B.Sc., M.Sc, PhD

Department of Endocrinology, Centre of Postgraduate Medical Education,

ul. Marymoncka 99/103, 01-813 Warsaw, Poland

Phone: (+48) 22 569 02 93, e-mail: piotr.glinicki@bielanski.med.pl

Conflict of interest: none declared
Abstract

The negative impact of even subtle maternal thyroid hormone deficiency on pregnancy outcome and intellectual development of 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 occurring during pregnancy the trimester-specific reference ranges for thyroid-stimulating hormone (TSH) and free thyroid hormones should be established, but because of inter-assay differences and other confounders including ethnicity and iodine intake such norms are reliable only for local populations and unique laboratory method. In turn, the fixed reference ranges suggested by endocrine societies may carry a risk of misclassification some healthy pregnant women to be hypothyroid. The value of levothyroxine treatment on pregnancy and children cognitive outcomes is not clear. Therapeutic benefits in decreasing miscarriage and preterm delivery rates were observed when intervention was held in the first trimester in women with TSH level 2.5-10 mU/l, mainly ≥4.0 mU/l. The possible harmful effect of treatment includes preterm delivery, gestational diabetes, hypertension and pre-eclampsia. The only three prospective, randomized, placebo controlled trials evaluating efficacy of levothyroxine therapy on children intelligence quotient were started in the second trimester, may be too late to demonstrate differences between treatment and placebo groups. Awaiting for the results of future trials clinician should be aware that low-dose levothyroxine 25-50 µg daily is probably not harmful and may be beneficial but mechanistic implementation of therapy in each pregnant women with TSH >2.5mU/l seems too simplistic.

Key words: diagnosis, pregnancy, subclinical hypothyroidism, treatment
Introduction

The significance of maternal thyroid hormone deficiency during pregnancy on child development was brought into endocrinologists attention over 20 years ago. In 1999 Haddow et al. demonstrated that untreated overt hypothyroidism in pregnant women may adversely affect neurodevelopment of the children [1]. Although none of them had hypothyroidism as newborns, their intelligence quotient (IQ) scores assessed at 7-9 year-old were 7 points lower and 19% of them had scores of 85 or less as compared with 5 % of the matched control children. In the same year Pop et al. documented that maternal free thyroxine (fT4) concentration below the 10th percentile accompanied with normal thyroid-stimulating hormone (TSH) at 12 weeks’ gestation caused significantly lower scores of development on the Bayley Psychomotor Developmental Index scale in the children at 10 months of age [2]. The relative risk (RR) for impaired psychomotor development was 5.8; 95% confidence interval (CI), 1.3-12.6. These results had been confirmed in 2003 by the same group of authors 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 fT4 concentration increased during the further course of pregnancy. From that time a large literature describing the impact of maternal overt and subclinical hypothyroidism (SH) on adverse obstetric and neonatal outcomes have been published. Many reports demonstrated that SH during pregnancy is associated with increased risk of miscarriage, preterm delivery, placental abruption, gestational diabetes, hypertensive disorders of pregnancy, pre-eclampsia, intrauterine 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]. These inconsistent results may be related to a different criteria of SH diagnosing, co-existence of anti-thyroid antibodies which are attributable to be an independent risk factor for pregnancy adverse outcomes, different maternal age of the studied groups and various gestational age of
thyroid function evaluation. A similar inconsistency can be observed among maternal SH during pregnancy and neurodevelopmental disorders in children accessed as reduced intelligence scores, autism and attention deficit hyperactivity disorder (ADHD). In a 2018 meta-analysis based on 11 studies published between 1999 to 2015 a significant relationship between maternal SH during the first half of pregnancy and intellectual disability in early childhood was demonstrated. The odds-ratio (OR) of the risk of the cognitive developmental disorder was 2.14; 95% CI, 1.2 - 3.83; \(P = 0.01\) [27]. The poorer neurodevelopment including lower IQ and motor scores, declined vision development, decrement in general cognitive index were noted at 6 and 25-30 months of age and later at 5-8 years of age.

Williams et al. demonstrated in children at 5.5 years of age a 3.2 points decrement in general cognitive index for each milliliter per liter increment in maternal TSH [28]. However, in several studies no link between maternal SH and offspring intellectual deficits accessed 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 demonstrated based on 3 and 5 publications respectively [27]. However, in the recent case-cohort study of Andersen et al. an increased risk of autism spectrum disorder was observed with hazard ratio (HR) 1.7; 95% CI, 1.04-2.75, but no relation was found between maternal SH and ADHD and epilepsy [33]. Taking these facts all together there is a strong suggestion, that maternal SH during pregnancy has a deleterious impact on obstetric and children neurodevelopmental outcomes. Unfortunately, many uncertainties concerning diagnosis and treatment of SN have been arised.

**How to recognize subclinical hypothyroidism in pregnancy**

Pregnancy profoundly change thyroid function and thyroid hormones metabolism therefore reference ranges for thyroid function tests (TFTs) in pregnant women differ from that in nonpregnant population and among trimesters. Placental human chorionic gonadotropin
(hCG), which exhibits structural similarity to TSH and 1/4000th thyrotropic activity of TSH stimulates thyroid gland directly through TSH receptor. HCG reaches the highest level at about 10 weeks’ gestation and in the second and third trimester decreases to a plateau. There is an inverse relationship between hCG and TSH throughout pregnancy: the first trimester peak of hCG corresponds to the reduction of TSH secretion, then TSH slightly raises during the second and third trimester but does not reach the pre-pregnancy values. Therefore, the upper and lower TSH normal limit decreases, changes by trimester and its secretion can be transiently suppressed. As a consequence of hCG stimulation serum concentrations of fT4 and free triiodothyronine (fT3) increase during the first trimester but in the further course of pregnancy its values decrease because of transplacental transfer to the fetus, degradation by the placental iodothyronine deiodinase type III and increased renal filtration.

The range of normal serum total T₄ (TT₄) and T₃ (TT₃) during pregnancy is augmented because of rapid increase in thyroxine-binding globulin (TBG) levels. Therefore, in the second and third trimester the nonpregnant TT₄ and TT₃ range should be multiplied by 1.5-fold.

SH is defined as a presence of elevated serum TSH with normal fT4 or TT4 values but determining the upper normal TSH limit in 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, that the most valid reference ranges for TSH and thyroid hormones are those established by medical centers for local population of healthy, iodine-sufficient, thyroid peroxidase antibody (TPOAb) negative pregnant women without thyroid illness [34-36]. Implementing these recommendations may be difficult, because TSH and to some extend fT4 does not exhibit a Gaussian distribution and is skewed toward upper values so that a minimum of 400 individual measurements is required to create reference intervals [37].
Another limitation of such population-derived reference ranges is that they are assay-specific. Springer et al. demonstrated that TSH reference ranges established simultaneously with 7 different analytical systems representing immunoassays most often used world-wide in 229 women being in early pregnancy may vary from 0.18-2.78 mU/l to 0.25-3.9 mU/l [38]. McNeil and Stanford in their elegant review documented that trimester-specific TSH 97.5 \textsuperscript{th} percentiles differed among the assays used and fell into two groups- according to Architect, Beckman and Immulite first trimester TSH 97.5 \textsuperscript{th} percentiles were around 3.0 mU/l whilst according to Centaur and Roche were closer to 4.0 mU/l. Only 4 out of 27 studies reported this value to be close to 2.5 mU/l [39]. However, other authors did not confirm important inter-assay differences for TSH but pointed out a great inter-assay dependance of fT4 measurements: up to 100% fT4 levels determined by one immunoassay as normal were outside the reference range established by another immunoassay [40]. It means, that patient results obtained by particular analytical method should be referred to the reference ranges obtained by the same assay, otherwise a serious misclassification can happen.

Trimester- and assay-specific reference intervals for TSH should not be adopted from one population to another in an uncritical way. 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 the lower median TSH in black pregnant women than in the white ones was found: 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, the Asian women had the highest TSH concentrations.

In the 2 studies from Netherlands the higher mean TSH values were found in Dutch women in comparison to Moroccan, and Surinamese women, according to Korevaar et al.: 1.5 vs 1.29 and 1.33 mU/l respectively [45,46]. As suggested by Peters et al. these differences may be due to the distinct thyroid-pituitary set-points among the people of various ethnic backgrounds and also in different hCG levels [47].
Iodine dietary supply, the essential substrate for thyroid hormone synthesis is another important factor influencing TFTs. Iodine requirement in pregnancy increases by 50% concurrently with 50% increase in thyroid hormone synthesis: from 150 µg in nonpregnant adult population to 250 µg daily. According to the recommendations of the World Health Organisation urinary iodine concentration (UIC) of 150–249 µg/l is a good indicator of an adequate iodine intake in pregnant populations but not in the individual patient. Some papers, but not all, documented that iodine deficiency particulary severe increases TSH in pregnancy [48]. However, more than adequate (UIC>250-499 µg/l) and excessive iodine intake (UIC>500 µg/l) can also exert deleterious effect on thyroid function resulting in augmentation of TSH and diminution of fT4 concentration and increasing the SH prevalence [48,49].

Different thyroid results can be also 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.

Body mass index (BMI) can be another factor influencing TFTs in pregnancy. Several observations documented higher TSH and lower fT4 concentrations in pregnant women with BMI >25-30 kg/m² [51-53].

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

Age might be another confounding factor influencing TSH results: its levels can increase with age and according to the observations made by Pearce and al. in pregnant women TSH increased by 0.03 mU/l for every year of maternal age ($P = 0.03$) [58,60].

As demonstrated by Bestwick et al. the problems of inter-assay, ethnic and maternal weight differences in TSH and fT4 can be overcome by using multiple of medians (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 specific population. For instance, Bestwick and colleagues calculated an increase in TSH of 0.025 MoMs and decrease in fT4 of 0.009 MoMs per 10-kg increase in body weight [61].

The trimester-specific reference ranges of TSH and free thyroid hormones for Polish population by using electrochemiluminescent metod were established in multicenter study and presented in Table 2 [62].

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 to use the reference ranges obtained from similar patient populations [36]. If such norms are inaccessible the Polish and international endocrine societies recommend to use fixed reference intervals based on published studies (Table 3). According to 2011 ATA, 2012 Endocrine Society (ES), and 2014 European Thyroid Association (ETA) the upper normal limit for TSH is quite similar: 2.5 mU/l for the first trimester, 3.0 mU/l for the second and 3.0-3.5 mU/l for the third trimester [35,63,64]. In 2017 ATA issued new guidelines with fixed TSH reference intervals up to 4.0 mU/l for each trimester of pregnancy [36]. These new cut-offs have been derived based on the recent data from India, China, Korea, US and Netherlands showing only modest TSH reduction in the first-trimester upper reference limit of 0.5-1.0 mU/l occurring at weeks 7-12. Interestingly, similar observation was made by the Danish authors [65]. When analysing TSH and fT4 set-point in pregnant women the authors of 2017 ATA recommendations stated that a significant fT4 reduction had occurred only when the serum TSH was higher than 4.8 mU/l.

The use of previously recommended fixed TSH upper-limit cut-offs of 2.5-3.0 mU/l could lead to misclassification of some healthy pregnant women as having SH. According to Medici
et al. 8.6 % and 4.9% of healthy, TPOAb-negative pregnant women with TSH within population-derived reference range had TSH values above 2.5 and 3.0 mU/l in the first and second trimester respectively [66]. Even higher rate of misclassification was reported by Li et al.: 27.8 % of Chinese pregnant women in the first trimester had TSH above 2.5 mU/l whilst only 4% of them had TSH above upper limit of population-based reference intervals [67].

A various criterion of establishing upper normal limit of TSH have also influenced the reported prevalence of SH in pregnancy: from 1.5%- 42.9% according to 2018 meta-analysis including fifty-six studies [68]. After pooling samples SH prevalence was 3.47% among studies using population-derived 97.5th percentile TSH cut-off, 14.39% when 2011ATA TSH cut-offs were used and 4.05% when 2017ATA TSH cut-offs were adopted.

Estimation of fT4 serum concentration in pregnancy carries even a greater challenge than TSH. The commonly used indirect commercial tests are much dependent on serum binding-proteins including thyroxine-binding globulin and albumins and also on free-fatty acids. Thyroxine-binding globulin and free-fatty acids typically rise during pregnancy whilst albumins decrease, consequently, these tests can give falsely high or falsely low results. Similarly, to TSH results, fT4 measurements exhibit inter-assay differences and may be influenced by ethnic features, maternal weight, age and smoking habits: lower fT4 levels were observed in pregnant women according to increasing BMI, age and among smokers [55,58,59].

Nowadays, the reference method which is free of commercial test limitations is measure of free thyroid hormones in the dialysate or ultrafiltrate using solid phase extraction–liquid chromatography/ tandem mass spectrometry (LC/MS/MS) [63]. However, this reference method is still unreachable in every-day clinical practice. The suggested alternative strategy to fT4 determinations is to measure TT4 concentration and use non-pregnant reference ranges...
(5-12 µg/dl or 50-150 nmol/l) multiplied by 1.5-fold or measure fT4 index (fT4I). The last 2 methods are infrequently used in European countries.

**Can L-thyroxine therapy prevent adverse pregnancy and neonatal outcomes of subclinical hypothyroidism?**

**Evidence for treatment benefits on pregnancy outcomes**

Although the huge data on negative impact of SH on pregnancy outcome has been gathered the evidence on L-thyroxine (L-T4) therapy benefits in reducing pregnancy complications is not clear. In 2010 in the prospective interventional trial Negro and colleagues evaluated the impact of levothyroxine therapy on TPOAb-positive pregnant women with TSH > 2.5 mU/l. Intervention was undertaken in the first trimester and levothyroxine dose was titrated to maintain TSH < 2.5 mU/l in first trimester and <3.0 mU/l in the second and third trimester. Levothyroxine therapy resulted in a significant decrease in a composite of adverse pregnancy outcomes [69]. In 2017 Nazarpour et al. assessed the results of levothyroxine treatment in the TPOAb-positive pregnant women without overt thyroid dysfunction. The dose of levothyroxine in the intervention group was TSH-dependant: 0.5 µg/kg daily for TSH <1.0 mU/l, 0.75 µg/kg daily for TSH between 1.0 and 2.0 mU/l, and a 1 µg/kg daily for TSH >2.0 mU/l or a TPOAb titer above 1500 IU/ml; dosages were maintained throughout gestation. In this prospective randomized small study including 65 treated and 66 untreated subjects the authors demonstrated that LT4 was beneficial in reducing the incidence of preterm delivery (RR 0.30; 95% CI, 0.1-0.85; \( P = 0.0229 \)) and newborn admissions to neonatal unit (RR 0.17; 95% CI, 0.04-0.73; \( P = 0.005 \)) but this effect was mainly observed in women with TSH ≥4 mU/l [70]. As TPOAb-positivity may be an independent confounder of the obtained results, in 2018 the same group of authors presented the effect of levothyroxine intervention in 366 pregnant women with SH who were TPOAb-negative. SH was defined as TSH levels within 2.5-10 mU/l. L-T4 treatment was started in the first trimester and resulted
in a significant reduction in the rate of preterm delivery in the group of women with TSH ≥ 4 mU/l (RR 0.38; 95% CI 0.15-0.98; \( P = 0.04 \)) but not in those with TSH 2.5-4 mU/l [71]. In Chinese prospective study by Zhao et al. conducted in 93 women with SH (TSH>2.5 mU/l in the first trimester; TSH>3.0 mU/l in the second trimester) patients were randomized to the 3 equal groups: treated at 8-10 weeks’ gestation, treated at 13-16 weeks’ gestation and untreated. The target TSH level during levothyroxine therapy was ≤ 3.0 mU/l. A significant reduction of overall pregnancy complications including gestational hypertension, pre-eclampsia, gestational diabetes and anemia was found in women treated with L-T4 at 8-10 weeks’ gestation compared to those treated at 13-16 weeks’ gestation and those who were untreated: 9.7% vs 41.9% vs 64.5%; \( P<0.01 \). When stratified with TPOAb status, in women who were TPOAb-positive, levothyroxine therapy diminished pregnancy complications even when started in the second trimester [72]. However, no benefits of treatment were reported in two other trials. Study issued by Casey et al. assessed the effect of L-T4 in 677 women with SH and 526 women with isolated hypothyroxinemia at a mean 16.7 weeks’ gestation. The reference ranges for gestational TFTs were population-derived: the TSH cut-off for SH was ≥ 4.0 mU/l and fT4 cut-off for hypothyroxinemia was < 0.8 ng/dl. The initial dose of L-T4 in women with SH was 100 µg daily and then the dose was adjusted to achieve the target TSH level of 0.1-2.5 mU/l. The effect of levothyroxine intervention was comparable to 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 study, Thyroid Antibodies and Levothyroxine Trial (TABLET) was designed to assess whether the use of levothyroxine would increase the rates of live births among euthyroid women with TPOAb. Nine hundred fifty two participants were recruited from among women with a history of at least one miscarriage or infertility. Euthyroidism was defined as TSH serum concentration 0.44-3.63 mU/l, which covered the second and third
quartiles of the 3 assays used. Treatment with 50 µg of L-T4 daily was intitiated in preconception period and continued throughout the pregnancy. There were no differences between the treatment and placebo groups in live-birth rate: 37.4% vs 37.9% (RR 0.97; 95% CI, 0.83-1.14; P = 0.74) nor 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 ≤ 2.5 mU/l and TSH >2.5 mU/l and no differences between intervention and placebo groups were noted according to primary and secondary outcomes [74].

In another study Maraka et al. analyzed the both: benefits and adverse effects of levothyroxine therapy for SH. In this retrospective cohort study of 5,405 pregnant women with TSH 2.5-10 mU/l and uncertain TPOAb status L-T4 therapy significantly diminished the incidence of pregnancy loss by 38% (P<0.01) but increased some pregnancy complications including preterm delivery (OR 1.60; 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, 1.10-2.37). The favorable effect of levothyroxine treatment was observed only in pregnant women with TSH 4.1-10 mU/l but not in those with TSH 2.5-4.0 mU/l. Moreover, in women with TSH 2.5-4.0 mU/l L-T4 treatment carried an increased risk of gestational hypertension comparing with untreated patients with the same range of TSH (OR 1.76; 95% CI 1.13-2.74). No significant interaction between pre-treatment TSH concentration and effect of thyroid hormone use on any other adverse pregnancy outcome was found [75]. In a similar retrospective study evaluating data of 3296 Chinese pregnant women Zhang and colleagues reported that L-T4 treatment provided in a subgroup of 266 subjects decreased the risk of miscarriage among women with TSH 2.5-4.08 mU/l (27.4% TPOAb- positive): OR 0.05; 95% CI: 0.01-0.35 and in the group of women with TSH 4.08-10 mU/l (34.2% TPOAb- positive) by 23% (P<0.001) but doubled the risk of gestational diabetes in the TSH 2.5-4.08 mU/l group: OR 1.80; 95% CI: 1.20-2.69) [22].
Conclusions of the results of the presented 8 studies (Table 4) are difficult because of different definition of TSH abnormality (> 2.5 mU/l; ≥ 4.0 mU/l; 2.5-10 mU/l), various TPOAb status (positive, partly positive, negative, uncertain), time of treatment intervention (first trimester, second trimester, uncertain), and target TSH (0.1-2.5 mU/l; <2.5 mU/l; ≤3 mU/l). Despite these discrepancies, it should be emphasized that in 6 out of 8 trials the positive effects of L-T4 treatment, mainly in diminishing the rate of pregnancy loss were observed. In 5 studies which demonstrated benefits of treatment, levothyroxine was instituted in the first trimester. The importance of early intervention was especially stressed by Zhao et al., who observed better results when the treatment was started at 8-10 weeks’ gestation comparing to 13-16 weeks’ gestation. However, in TABLET study which did not demonstrate levothyroxine benefits, intervention was instituted before conception.

In 5 out of 6 studies in which favourable effect of L-T4 treatment was found the population studied was TPOAb- positive, and only 1 paper documented benefits of treatment in TPOAb negative women but exclusively in those with TSH ≥ 4.0 mU/l and not in those with TSH 2.5-<4.0 mU/l. This leaves doubts whether implementation of therapy in pregnant women with TSH 2.5-upper normal limit who are TPOAb- negative might be beneficial and more observations in this group of women are needed.

The most intriguing point concerning SH in pregnancy is TSH level at which the medical intervention should be held and based on presented studies it remains unresolved primarily because of the various TPOAb status which carries an additional risk of pregnancy loss.

Unexpectedly, in 2 studies the adverse effects of L-T4 therapy were documented. However, Zhao et al. in their small prospective study observed beneficial effect of levothyroxine therapy in women with TSH> 2.5 mU/l in decreasing the rate of pregnancy
complications. The further studies on the possible levothyroxine therapy side-effects in pregnant women are essential.

*Evidence for treatment benefits on children cognitive outcomes*

There are 3 prospective randomized controlled trials assessing the influence of levothyroxine therapy for maternal SH on children IQ. The Controlled Antenatal Thyroid Screening (CATS) study randomized 880 pregnant women with TSH levels > 97.5th percentile (subclinical hypothyroidism) or fT4 < 2.5th percentile (isolated hypothyroxinemia) or both to levothyroxine treatment or placebo. Intervention was undertaken at a median gestational age of 13 weeks 3 days with the initial dose of 150 µg of L-T4 per day. Then the treatment was adjusted as needed to gain a target TSH level of 0.1 to 1.0 mU/l. In 10% of participants the initial dose of 150 µg of L-T4 was lowered because of over-dosage. Children cognitive function was assessed at 3 years of age and no difference was found between those whose mothers were treated (mean IQ 99.2) or untreated (mean IQ 100.0) during pregnancy (P=0.40). The percentage of children with an IQ of less 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 which measured IQ in the same group of children at age 9.5 years: 119 treated, 98 untreated and 232 children included from mothers with normal gestational TFTs. Interestingly, there was also no difference in IQ below 85 between children of mothers with normal and subnormal gestational TFTs (OR 1.15;95% CI, 0.52- 2.51; P = 0.73). Additional important observation coming from this trial was that over-supplementation of L-T4 resulting in fT4 level > 97.5th percentile had no detrimental effect on the percentage of children with IQ below 85 but significantly increased incidence of ADHD symptoms and behavioral difficulties [77]. In aferomentioned study of Casey et al. who assessed the effect of levothyroxine in 677 women with subclinical hypothyroidism and 526 women with hypothyroxinemia at a mean 16.7 weeks of gestation the primary outcome was the children IQ
score at 5 years of age. The authors found no difference in children IQ between L-T4 and placebo group. The median IQ of children from mothers with SH was 97 (95% CI, 94-99) in the levothyroxine 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. were criticized because of the late time of treatment initiation. In fact, in the both trials the intervention with levothyroxine was instituted and the 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 over-supplementation of levothyroxine coming from the study of Korevaar et al. The authors observed that both low (below 12.2 pmol/l) and high (above 20.1 pmol/l) maternal fT4 concentrations during early pregnancy (<18 weeks) were associated with lower child’s IQ and lower grey matter and cortex volume on MRI assessed at a 6-8 years of age [78].

**Recommendations for the management of subclinical hypothyroidism in pregnancy**

In the face of the inconsistent results of levothyroxine treatment for SH in pregnancy, the recommendations issued by national and international endocrine societies vary. PTE in the guidelines issued in 2011 recommends to treat women in preconception period when TSH levels are above 2-2.5 mU/l, especially in cases 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 preconception period was based mainly on reference intervals established by the American National Academy of Biochemical Chemistry in population of euthyroid healthy volunteers free from detectable TPOAbs or thyroglobulin antibodies and any personal or family history of thyroid dysfunction but not based on Polish population survey [79].

Similarly, in 2014 ETA released 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]. It should be underlined that the ETA arbitrarily established
upper normal limit for TSH was higher in the second and third trimester than that of PTE (3.0 and 3.5 vs 2.5 and 2.5 mU/l respectively).

The latest 2017 ATA guidelines take into account the both: TSH level and TPOAb status assuming that there is a synergistic negative effect of TPOAb and thyroid hormone deficiency on pregnancy outcome. ATA strongly recommends levothyroxine treatment for TPOAb-positive women with TSH above the pregnancy-specific upper normal range and to consider treatment for TPOAb-positive women with TSH between 2.5 mU/l-upper normal limit. In TPOAb-negative women the treatment is recommended when TSH level is ≥10 mU/l and advised to be considered when TSH level is above normal limit to below 10 mU/l. Pregnant women who are TPOAb-negative and have TSH levels between 2.5 mU/l- upper normal limit do not need treatment. The ATA arbitrarily proposed upper normal limit for TSH for each trimester of pregnancy is 4.0 mU/l and the target value of TSH during levothyroxine treatment is below 2.5 mU/l, which is quite different than the PTE and ETA proposals [36]. Although ATA guidelines do not define what is the normal TSH range in preconception period, but according to the American National Health and Nutrition Examination Survey III the normal TSH reference intervals for healthy reference population negative for thyroid antibodies and not taking androgens or estrogens is 0.47-4.15 mU/l [80].

In the sharp contrast to the recommendations issued by endocrine societies is the statement of the American Congress of Obstetricians and Gynecologists published in 2015 that currently, there is no evidence that identification and treatment of SH during pregnancy improves outcomes [81]. On the contrary, in the guidelines issued in 2015 by the Practice Committee of American Society for Reproductive Medicine there is a statement that treatment of SH defined as TSH> 4.0 mU/l is associated with improvement in pregnancy outcomes and miscarriage rates but insufficient evidence exists for treatment benefits of women with TSH 2.5-4.0 mU/l [82].
Summary and authors opinion

It must be emphasized, that several new trials have been published from the time the last guidelines were released and the next 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 fT4 for each trimester are needed to avoid a false-positive diagnosis and unnecessary treatment
- in the lack of such norms, taking into account Polish observations, the TSH upper limit for general population should be diminished by 1.0-1.5 mU/l in the first trimester and by 0.5-1.0 mU/l in the second and third trimester
- levothyroxine treatment introduced in the first trimester can prevent the pregnancy loss but may increase some pregnancy complications including preterm delivery, gestational diabetes, gestational hypertension and pre-eclampsia
- the most beneficial effect of treatment is probably achieved in women with TSH ≥ 4 mU/l and uncertain in TSH range 2.5-<4.0 mU/l, especially when TPOAb are negative
- because of the potential negative impact of levothyroxine treatment on the mother’s and child’s health which must be further explored, the precaution on levothyroxine over-dosage should be made and strict surveillance of maternal status and regular glucose measurements, for instance every 2 months are advised
- implementation of levothyroxine treatment in the second trimester does not improve intellectual development of the progeny
- new trials assessing the effect of levothyroxine treatment started early in the first trimester on children IQ are needed.

The great area of uncertainty still remains and concerns the following problems:
- do pregnant women TPOAb- negative with TSH 2.5-<4.0 mU/l benefit from levothyroxine treatment
- what is the target level of TSH during L-T4 treatment in pregnant women: \( \leq 2.5 \text{ mU/l} \) or below trimester-specific upper limits
- should not only TSH but also fT4 level be an important target of therapy, especially in the first trimester, to avoid the negative effect of the both: the low and the high fT4 values
- is TPOAb-positivity or previous pregnancy loss an indication to start L-T4 therapy at lower TSH levels: 2.5- 4 mU/l.

Our paper was intended to point out the controversies in diagnosing and treating 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 procedure and women with isolated gestational hypothyroxinemia although very important, is beyond the scope of this study.

Awaiting for the results coming from the future trials a clinician should probably be aware of the fact that in the difficult clinical situations implementation of a low-dose levothyroxine 25-50 µg daily is probably not harmful and may be beneficial but high fT4 levels might have a negative impact on pregnancy outcome, children IQ and behavioral problems.

References


Table 1. Meta-analysis and observational studies documenting association between maternal subclinical hypothyroidism during pregnancy and adverse obstetrical and neonatal outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
<th>OR (95%CI)</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al., 2015 [6]</td>
<td>Pregnancy loss, Preterm delivery, Placental abruption, Breech presentation at term</td>
<td>1.93 (1.40-2.64), 1.30 (1.05-1.60), 2.16 (1.15-4.06), 2.30 (1.50-3.51)</td>
<td></td>
</tr>
<tr>
<td>Maraka et al., 2016 [7]</td>
<td>Miscarriage/pregnancy loss, Preterm delivery, Placental abruption, Growth restriction, Pre-eclampsia, Gestational diabetes, Neonatal death</td>
<td>2.01 (1.66-2.44), 1.20 (0.97-1.50), 2.14 (1.23-3.70), 1.70 (0.83-3.50), 1.30 (1.00-1.68), 1.28 (0.90-1.81), 2.58 (1.41-4.73)</td>
<td></td>
</tr>
<tr>
<td>Tong et al., 2016 [8]</td>
<td>Growth restriction</td>
<td>1.54 (1.06-2.25)</td>
<td></td>
</tr>
<tr>
<td>Gong et al., 2016 [9]</td>
<td>Gestational diabetes</td>
<td>1.56 (1.29-1.88)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Condition</td>
<td>Odds Ratio (CI)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------</td>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Van den Boogaard et al., 2016 [10]</td>
<td>Pre-eclampsia</td>
<td>1.70 (1.10-2.64)</td>
<td></td>
</tr>
<tr>
<td>Observational studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karacosta et al., 2012 [12]</td>
<td>Growth restriction</td>
<td>3.10 (1.22-8.01)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gestational diabetes</td>
<td>4.33 (2.10-8.91)</td>
<td></td>
</tr>
<tr>
<td>Chen et al., 2014 [13]</td>
<td>Preeclampsia</td>
<td>2.24 (1.25-4.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Growth restriction</td>
<td>3.36 (1.75-6.38)</td>
<td></td>
</tr>
<tr>
<td>Ying et al., 2016 [14]</td>
<td>Gestational diabetes</td>
<td>1.81 (1.08-1.73)</td>
<td></td>
</tr>
<tr>
<td>Arbib et al., 2017 [15]</td>
<td>Preterm delivery</td>
<td>1.81 (1.02-3.28)</td>
<td></td>
</tr>
<tr>
<td>Vrijkotte et al., 2017 [16]</td>
<td>Large for gestational age in males</td>
<td>1.95 (1.22-3.11)</td>
<td></td>
</tr>
<tr>
<td>Carty et al., 2017 [17]</td>
<td>Lower birth weights</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furukawa et al., 2017 [18]</td>
<td>Gestational diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al., 2018 [19]</td>
<td>Preterm delivery</td>
<td>4.58 (1.46-14.40)</td>
<td></td>
</tr>
<tr>
<td>Wu et al., 2019 [21]</td>
<td>Hypertensive disorders</td>
<td>4.04 (1.85–8.84)</td>
<td></td>
</tr>
<tr>
<td>Zhang et al., 2020 [22]</td>
<td>Miscarriage</td>
<td>3.53 (1.85-6.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maternal composite outcomes</td>
<td>2.19 (1.26-3.81)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI- Confidence Interval; OR- Odds Ratio; RR- Relative Risk;
Table 2. Population-derived, trimester-specific reference ranges for thyroid-stimulating hormone, free thyroxine and free triiodothyronine established for Polish population by using electrochemiluminescent method, Elecsys (Roche)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Thyroid function test</th>
<th>General population</th>
<th>Pregnant women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I trimester</td>
</tr>
<tr>
<td>TSH, mU/l</td>
<td>0.3-4.5</td>
<td>0.009-3.177</td>
</tr>
<tr>
<td>fT3, pmol/l</td>
<td>3.1-6.8</td>
<td>3.63-6.55</td>
</tr>
<tr>
<td>fT4, pmol/l</td>
<td>11-22</td>
<td>11.99-21.89</td>
</tr>
</tbody>
</table>


Abbreviations: fT3, free triiodothyronine; fT4, 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

<table>
<thead>
<tr>
<th>Authors of recommendation</th>
<th>TSH (mU/l)</th>
<th>I trimester</th>
<th>II trimester</th>
<th>III trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polish Endocrine Society, 2011 [34]</td>
<td>-2.5</td>
<td>-2.5</td>
<td>-2.5</td>
<td></td>
</tr>
<tr>
<td>American Thyroid Association, 2011 [56]</td>
<td>0.1-2.5</td>
<td>0.2-3.0</td>
<td>0.3-3.0</td>
<td></td>
</tr>
<tr>
<td>Endocrine Society, 2012 [57]</td>
<td>-2.5</td>
<td>-3.0</td>
<td>-3.5</td>
<td></td>
</tr>
<tr>
<td>European Thyroid Association, 2014 [35]</td>
<td>-2.5</td>
<td>-3.0</td>
<td>-3.0</td>
<td></td>
</tr>
<tr>
<td>American Thyroid Association, 2017 [36]</td>
<td>-4.0</td>
<td>-4.0</td>
<td>-4.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TSH, thyroid-stimulating hormone

Table 4. Effects of levothyroxine treatment for subclinical hypothyroidism on pregnancy outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Definition of subclinical hypothyroidism</th>
<th>Time of intervention</th>
<th>Treatment outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro et al., 2010 [69]</td>
<td>Prospective, randomized</td>
<td>TSH&gt;2.5 mU/l and normal fT4</td>
<td>First trimester</td>
<td>Decrease in composite of adverse pregnancy outcomes</td>
<td>Population positive for TPOAb</td>
</tr>
<tr>
<td>Nazarpour et al., 2017 [70]</td>
<td>Prospective randomized</td>
<td>TSH 2.5-10 mU/l and normal fT4I: 1-4.5</td>
<td>First trimester</td>
<td>Decrease in incidence of preterm deliveries and newborn admissions to</td>
<td>Population positive for TPOAb, beneficial effect of treatment only when</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>TSH Range</td>
<td>Additional Details</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------------------------</td>
<td>-----------</td>
<td>-------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casey et al., 2017</td>
<td>Prospective randomized placebo-controlled</td>
<td>TSH≥4.0 mU/l and normal fT4: 11-24 pmol/l</td>
<td>Mean 16.7 weeks of gestation, no beneficial effects of treatment on pregnancy and neonatal outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TPOAb status uncertain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maraka et al., 2017</td>
<td>Retrospective</td>
<td>TSH 2.5-10 mU/l</td>
<td>Uncertain decrease in rate of pregnancy loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TPOAb status uncertain, beneficial effect of treatment only when TSH 4.1-10 mU/l but not in cases with TSH 2.5-4.0 mU/l, increase of incidence of preterm delivery, gestational diabetes, gestational hypertension and pre-eclampsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nazarpour et al., 2018</td>
<td>Prospective randomized</td>
<td>TSH 2.5-10 mU/l and normal fT4I: 1-4.5</td>
<td>First trimester, decrease in rate of preterm delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Population negative for TPOAb, beneficial effect of treatment only when TSH≥4.0 mU/l but not in cases with TSH 2.5-4.0 mU/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhao et al., 2018</td>
<td>Prospective, randomized</td>
<td>TSH&gt;2.5 mU/l in first trimester, &gt;3.0 mU/l in second trimester</td>
<td>First or second trimester, reduction of overall pregnancy complications including gestational hypertension, pre-eclampsia, anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Population positive for TPOAb in 32%, beneficial effect in women with TSH&gt; 2.5 mU/l treated at 8-10 weeks gestation compared to those treated at 13-16 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>TSH range</td>
<td>Timepoint</td>
<td>Effect</td>
<td>Population</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------</td>
<td>-----------</td>
<td>-------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Dhillon-Smith et al., 2019</td>
<td>Prospective, randomized double-blind placebo-controlled</td>
<td>TSH &gt; 2.5-3.6 mU/l</td>
<td>Pre-conception period</td>
<td>No beneficial effect of treatment on the rate of live-birth, pregnancy loss, preterm delivery, or in neonatal outcomes</td>
<td>Population positive for TPOAb</td>
</tr>
<tr>
<td>Zhang et al., 2020</td>
<td>Retrospective</td>
<td>TSH 2.5-10.0 mU/l, normal fT4</td>
<td>First trimester</td>
<td>Reduction in the incidence of miscarriage</td>
<td>Population positive for TPOAb in 27.4%, beneficial effect of treatment also when 2.5-4.8 mU/l but increased risk of gestational diabetes</td>
</tr>
</tbody>
</table>

Abbreviations: TSH, thyroid-stimulating hormone; fT4I, free thyroxine index; TPOAb, thyroid peroxidase antibodies