Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits

Zeeshan Javed and Thozhukat Sathyapalan

Ther Adv Endocrinol Metab

2016, Vol. 7(1) 12–23

DOI: 10.1177/2042018815616543

© The Author(s), 2015. Reprints and permissions: http://www.sagepub.co.uk/journalsPermissions.nav

***Abstract*:** Subclinical hypothyroidism (SCH) is defined as elevated thyroid stimulating hormone (TSH) with normal levels of free triiodothyronine (FT3) and free thyroxine (FT4). SCH is further classified into a milder condition with TSH levels between 4.0 and 10.0 milli-international units (mIU)/l (mild-SCH) and a severe form with TSH >10.0 mIU/l (severe-SCH). SCH is a common problem (prevalence is greater in women than men), which increases further with increasing age and TSH levels. Even though the risk of progression to overt hypothyroidism is higher in patients with severe-SCH, the risk is also significant in patients having mild-SCH; it has been suggested that every twofold rise in serum TSH would increase the risk from 1 to 4%, which further increases to 38% if thyroid antibodies are positive. Current data have shown increased cardiovascular risk in patients with mild-SCH and have demonstrated some benefits of levothyroxine treatment in reducing these events. However, evidence on the association of mild-SCH and musculoskeletal system, cognitive dysfunction, mood disorders, dyslipidaemia, diabetes and goitre is conflicting. Similarly, the discussion regarding the exact upper limit of normal for serum TSH remains controversial. The data have also shown increased risk of adverse pregnancy outcomes in patient with mild-SCH, with some benefits of thyroxine treatment. The recent available guidelines related to management of patients with serum TSH <10 mIU/l have suggested decisions should be made taking into account the age of the patient, associated risk factors and comorbid conditions. This chronicle review assesses current evidence regarding the risks associated and the recommendations related to benefits of levothyroxine treatment in patients having mild-SCH.

Keywords: associated risks, levothyroxine benefits, management, subclinical hypothyroidism, thyroid stimulating hormone

Introduction

It is well known that subclinical hypothyroidism (SCH) is a strong risk factor for the development of overt hypothyroidism in addition to older age, antithyroid antibodies and female sex. The risk of developing overt hypothyroidism rises with increase in thyroid stimulating hormone (TSH) levels as mentioned in the Whickham survey [Vanderpump *et al.* 1995; Helfand *et al.* 2004]. The risk is 57% and 71% for a 50 years-old female with a TSH level of 6 milli-international unit (mIU)/l and 9 mIU/l, respectively, over 20 years compared with only 4% in females who have TSH within the normal range [Vanderpump *et al.* 1995].

SCH is generally classified into a milder condition with TSH levels between 4.0 and 10.0 mIU/l (mild-SCH) and a severe form with TSH >10.0 mIU/l (severe-SCH) [Pearce *et al.* 2013]. It is also worth remembering that TSH values in both healthy individuals and patients with SCH vary throughout the day, with higher values in the evening and night. It is therefore recommended to repeat the thyroid function tests at least 3 months apart to make a firm diagnosis [Pearce *et al.* 2013]. There is also evidence suggesting that TSH elevation in people >80 years of age should be considered a physiological adaptation to aging and that an age-specific range for TSH should be considered when making diagnosis of

Correspondence to:
Dr Zeeshan Javed, MBBS
Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, University of Hull, Hull and East Yorkshire NHS Trust, Brocklehurst Building, Hull Royal Infirmary, Hull, HU3 2RW, UK
Zeeshan.javed@hyms.ac.uk

Thozhukat Sathyapalan, MD, FRCP
Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, University of Hull, Hull and East Yorkshire NHS Trust, Hull, UK

SCH [Surks and Hollowell, 2007]. It has been shown that almost 80% of patients with SCH were anti-thyroid peroxidase (TPO) antibodies positive and 80% of people who were diagnosed as having SCH had TSH <10.0 mIU/l [Fatourechi, 2009].

Levothyroxine treatment is generally recommended appropriate when the TSH level is >10.0 mIU/l. However, the available evidence on the risks and benefits of treatment for patients having TSH <10.0 mIU/l (mild-SCH) remains controversial and there is still no consensus regarding the clinical importance of adverse events and the benefits of thyroxine treatment in patients having TSH <10.0 mIU/l. One of the reasons could be that all the studies assessing the adverse effects had SCH patients having different levels of TSH and thyroid dysfunction [Fatourechi, 2009].

In this article, the current evidence available on the proposed adverse effects of mild-SCH and the benefits of screening and treatment of mild-SCH is reviewed.

Aetiology of SCH

The most common endogenous cause of SCH is considered to be chronic autoimmune thyroiditis (Hashimoto's thyroiditis) associated with anti-TPO antibodies [Baumgartner *et al.* 2014]. Other endogenous and exogenous causes include: TSH receptor loss of function mutations; recent adjustment in dose of levothyroxine especially in patients who are less compliant; transient TSH elevation during recovery from severe illness and subacute or postpartum thyroiditis; untreated primary adrenal insufficiency; during treatment with various drugs (lithium, amiodarone, recombinant human TSH injections); and presence of heterophile antibodies [Surks *et al.* 2004; Pearce *et al.* 2013].

Outcome of SCH with TSH <10.0 mIU/l (mild-SCH) in adults

Risk of progression to overt hypothyroidism

The first study to look at the long-term incidence of overt hypothyroidism was the Whickham survey [Vanderpump *et al.* 1995] which found that a rise of serum TSH above 2 mIU/l was associated with increased risk of hypothyroidism, which increased further if anti-TPO antibodies were positive. The survey found that a twofold rise in serum TSH would increase the probability from 1 to 4% and this risk further increased to 38% if positive for anti-TPO antibodies [Vanderpump *et al.* 1995]. Similarly, another recent study showed that the rate of progression to overt hypothyroidism was more in patients having TSH >10 mIU/l but, for those who had TSH between 4.5 and 10.0 mIU/l, the rate was higher in those who were anti-TPO antibodies positive. The resolution of SCH at the end of 2 years was more (46%) in those with TSH of 4.5–6.9 mIU/l compared with those with high TSH levels (10% for TSH of 7–9.9 mIU/l) [Somwaru *et al.* 2012]. In another study, both male and female patients aged >55 years were followed for up to 72 months and it was found that the TSH level normalized in 52% of those patients who had serum TSH between 5.0 and 9.9 mIU/l [Diez and Iglesias, 2004]. However, the increase in TSH levels with advancing age and the upper limit of the TSH reference range are still controversial and under debate [Spencer *et al.* 2007; Baumgartner *et al.* 2014].

Symptoms of hypothyroidism

Most of the patients with mild-SCH are asymptomatic and only few of them have typical hypothyroid symptoms. A large questionnaire-based study on 25,862 patients showed a significant difference, although small, in symptoms between euthyroid and SCH patients [Canaris *et al.* 2000; Pearce *et al.* 2013]. The most frequent symptoms reported were problems with memory, slowness of thinking, muscle cramps, muscle weakness, tiredness, dry skin, feeling colder, hoarseness of voice, puffy eyes and more constipation [Canaris *et al.* 2000]. Jorde and colleagues found that there was no difference in symptoms of hypothyroidism between SCH patients having TSH <10 mIU/l compared with healthy controls except tiredness [Jorde *et al.* 2006]. A recent review looked at the current evidence and found no significant difference in symptoms in patients with SCH and euthyroid controls [Joffe *et al.* 2013].

The randomized trials which looked at the effect of levothyroxine therapy in patients having mild-SCH are considered insufficient to support levothyroxine treatment in this group and the benefits seen in the available trials are either very minor or of no benefit [Baumgartner *et al.* 2014]. One of the studies which compared the beneficial effects of levothyroxine treatment in SCH patients having TSH between 5.0 and 10.0 mIU/l with placebo found no benefit [Kong *et al.* 2002]. Similarly, many other recent studies have not

shown any improvement in symptoms such as anxiety, mood and cognition in elderly patients [Gussekloo *et al.* 2004; Fatourechi, 2009]. However, there is also some evidence of benefits regarding symptom improvement (especially tiredness) with levothyroxine treatment in patients having TSH <10 mIU/l [Razvi *et al.* 2007]. In summary, most patients with mild-SCH have either very few symptoms or no symptoms and there is some evidence, albeit insufficient, of improvement in tiredness by levothyroxine treatment [Pearce *et al.* 2013].

Obesity, diabetes and dyslipidaemia

Several studies had shown a positive association between body mass index (BMI) and increase in TSH levels even after correcting for age, menopausal status and smoking [Nyrnes *et al.* 2006; Fox *et al.* 2008; De Moura Souza and Sichieri, 2011; Kitahara *et al.* 2012] and showed there was increase in weight of 1.1 kg in men and 2.3 kg in women for every increase in log TSH. Conversely, several studies showed substantial weight loss resulted in a decrease in TSH levels [Chikunguwo *et al.* 2007; Dall'asta *et al.* 2010]. Current evidence suggests that a causal relationship between obesity and SCH is not anticipated because studies have shown that TSH levels reverted to normal upon reduction of weight and current European Thyroid Association (ETA) guidelines suggest there is no evidence available in favour of beneficial effects of levothyroxine on body weight in obese subjects having SCH with TSH <10 mIU/l [Pearce *et al.* 2013].

The studies have indicated that risk of SCH is 30% in patients having type 1 diabetes mellitus; this risk increases to 50% if there is associated Addison's disease [Perros *et al.* 1995; Triolo *et al.* 2011; Kahaly, 2012]. Based on these facts, ETA guidelines [Pearce *et al.* 2013] have suggested once yearly TSH monitoring in patients with type 1 diabetes. SCH had also been shown to be associated with insulin resistance [Stanicka *et al.* 2005] and in patients with type 2 diabetes mellitus having SCH, worsening of glycaemic control warrants a trial of levothyroxine [Skarulis *et al.* 2010; Pearce *et al.* 2013].

Several studies have investigated the relationship between SCH and lipid abnormalities and have found that SCH is associated with high triglycerides (TGs), total cholesterol (TC) and LDL cholesterol (LDL-C). These effects are more pronounced in patients with TSH >10 mIU/l, but few studies have observed abnormal lipids in patients with mild-SCH [Canaris *et al.* 2000; Boekholdt *et al.* 2010]and found that even a 1.0 mIU/l increase in TSH resulted in a subsequent rise in TGs, TC and LDL-C [Bindels *et al.* 1999]. Similarly, trials have observed heterogeneous effects of levothyroxine therapy on lipid profile in patients having SCH. Although effects are more pronounced in patients with initial TSH >10 mIU/l, few trials have also revealed significant improvements in lipid profile after levothyroxine treatment in patients with TSH <10 mIU/l, thus reducing cardiovascular risk [Caraccio *et al.* 2002; Monzani *et al.* 2004; Razvi *et al.* 2007].

Cardiovascular events, mortality and heart failure

It is well known that thyroid hormones act on the heart and vasculature. Research has been conducted recently to determine the effects of SCH on the cardiovascular system [Baumgartner *et al.* 2014]. Although the initial analysis of the Whickham survey did not show any increased risk of coronary heart disease (CHD), re-analysis of the data looking specifically at patients with SCH showed increased CHD events and mortality [Vanderpump *et al.* 1995]. The Rotterdam Study also showed that SCH is an independent risk factor for myocardial infarction (MI) and atherosclerosis in elderly women patients with an average TSH of 5.8 mIU/l, especially if they are positive for anti-TPO antibodies [Hak *et al.* 2000]. The increased risk of CHD has also been associated with mild-SCH in a recent meta-analysis of observational studies, albeit the risk was more in patients having TSH >10 mIU/l [Rodondi *et al.* 2006; Ochs *et al.* 2008; Fatourechi, 2009]. The studies have also shown that SCH (mean TSH range <7 mIU/l) can lead to: functional cardiac abnormalities, such as impaired systolic and diastolic cardiac function (Table 1); and vascular dysfunction with impaired endothelial function and increased vascular stiffness [Monzani *et al.* 2001; Razvi *et al.* 2007; Baumgartner *et al.* 2014]. One of the meta-analysis showed that the increased risk of ischemic heart disease and cardiovascular mortality is only prevalent in the younger population [Razvi *et al.* 2008]. Some studies have not shown an increased risk of CHD and mortality in patients with mild-SCH, but there was a trend of increasing risk with rising TSH; it shown that that there was no association between SCH and overall mortality in the elderly but that there was even

Table 1. Risk of cardiovascular events in SCH patients with TSH between 4.5 and 9.9 mIU/l.

TSH level	HR for CHD events (95% CI)	HR for CHD mortality (95% CI)	HR for heart failure events (95% CI)
TSH 0.45–4.49 mIU/l	1.00 (reference)	1.00 (reference)	1.00 (reference)
TSH 4.5–6.9 mIU/l	1.00 (0.86–1.18)	1.09 (0.91–1.30)	1.01 (0.81–1.26)
TSH 7.0–9.9 mIU/l	1.17 (0.96–1.43)	1.42 (1.03–1.95)	1.65 (0.84–3.23)

Adapted from Baumgartner *et al*. [2014].
CI, confidence interval; CHD, coronary heart disease; HR, hazard ratio; mIU, mill-international unit; TSH, thyroid stimulating hormone.

a reduction in the risk of mortality and cardiovascular problems in patients aged >85 years [Gussekloo *et al.* 2004; Baumgartner *et al.* 2014]. Similarly, a recent, large-scale retrospective cohort study looking at the effects of levothyroxine treatment on MI, cardiovascular death and all-cause mortality in patients with SCH found no beneficial effects except in patients under the age of 65 years [Andersen *et al.* 2015].

The increased risk of cardiovascular risk can be explained by several mechanisms: elevated TC and dyslipidaemia; high blood pressure; higher prevalence of metabolic syndrome; endothelial dysfunction; insulin resistance; and increased intima-media thickness of carotids, hypercoagulability and oxidative stress [Monzani *et al.* 2001; Razvi *et al.* 2007; Liu *et al.* 2010; Baumgartner *et al.* 2014].

In a systemic review, 6 out of 13 studies with patients with a mean TSH 4.8–9.8 mIU/l showed levothyroxine treatment resulted in an improvement in associated high total and LDL cholesterol [Danese *et al.* 2000]. These findings were confirmed by a recent, randomized, double blind, crossover trial in patients having SCH with a mean TSH of 6.6 mIU/l, which showed that levothyroxine treatment leads to significant improvement in many cardiovascular risk factors including total and LDL cholesterol [Razvi *et al.* 2007]. Several other studies have also shown significant improvement in cardiovascular risk markers after thyroxine treatment including improvement in endothelial function and carotid intima-media thickness [Monzani *et al.* 2001; Razvi *et al.* 2007]. Few studies have also shown that levothyroxine treatment in mild-SCH resulted in improvement of cardiac systolic function, diastolic function at rest and during exercise, cardiac preload, systemic vascular resistance and arterial stiffness [Monzani *et al.* 2001; Biondi, 2007; Pearce *et al.* 2013].

In summary, current evidence suggests that increased cardiovascular risk in patients having TSH <10 mIU/l is well established in the younger adult population (<70 years) [Kvetny *et al.* 2004; Walsh *et al.* 2005; Razvi *et al.* 2008; Rodondi *et al.* 2010] and recent prospective data analysis suggested that levothyroxine replacement therapy in patients with SCH was associated with less CHD risk in the younger population but not in the elderly population (>75 years) [Razvi *et al.* 2012]. Also, recent reports suggested that mild-SCH was even associated with longevity and could be beneficial in the elderly population (>70–85 years) [Gussekloo *et al.* 2004; Rozing *et al.* 2010; Pearce *et al.* 2013]. Further randomized controlled trials (RCTs) of levothyroxine treatment have been recommended to assess cardiovascular endpoints in various age classes. Few studies are already in progress to resolve these uncertainties [Mooijaart, 2012; Rodondi and Bauer, 2013].

Musculoskeletal system and exercise capacity

The current evidence suggests that patients with mildly raised TSH (<10 mIU/l) suffer more often from myalgia and weakness associated with reduced muscle strength and exercise capacity [Brennan *et al.* 2006; Reuters *et al.* 2009]. Possible mechanisms put forward were increased oxygen requirements during exercise and increased prevalence of anaemia in these patients [Mainenti *et al.* 2009]. However, a few studies did not show any reduction in functional capacity and even showed better mobility in patients with mildly raised TSH compared with euthyroids [Simonsick *et al.* 2009; Virgini *et al.* 2014]. One recent trial has shown that levothyroxine replacement with TSH normalization in these patients resulted in improved submaximal cardiopulmonary exercise performance with enhanced ability to perform daily life activities [Mainenti *et al.* 2009].

Two prospective studies [Lee *et al.* 2010; Svare *et al.* 2013] have shown increased risk of hip fracture in both men and women in patients with mild-SCH, which could be due to direct effects of TSH on bone metabolism through inhibition of both osteoclasts and osteoblasts [Baumgartner *et al.* 2014]. But there are no trials showing whether treatment with levothyroxine reduces this risk or not.

Mood disorders/cognitive dysfunction

The evidence related to association between mood disorders, cognitive dysfunction and mild-SCH is conflicting. The reasons suggested for the inconsistent results of these studies are different study designs, relatively smaller size, the age groups recruited were heterogeneous and different neurocognitive tests were used [Pearce *et al.* 2013]. There were two cross-sectional studies which showed impairment in memory and cognitive functions in patients having mild-SCH [Baldini *et al.* 1997; Del Ser Quijano *et al.* 2000; Pearce *et al.* 2013]. Trials also showed improvement in both verbal and spatial memory when TSH levels were normalized in patients with SCH by levothyroxine replacement [Correia *et al.* 2009; Aghili *et al.* 2012]. However, there were studies which revealed there was neither any association between cognitive impairment and mild-SCH [Parsaik *et al.* 2014] nor any benefit of levothyroxine replacement therapy on memory and cognition in these patients [Parle *et al.* 2010; Pearce *et al.* 2013]. The recent ETA guidelines recommend levothyroxine replacement in younger patients having mild-SCH with associated mild memory impairment and mood problems but available data do not suggest benefits in treating the elderly (>65 years) [Pearce *et al.* 2013].

Goitre and thyroid cancer

One recent systematic review showed a modest association of goitre with SCH [Monzani *et al.* 2013] which is contrary to previous observation in the Whickham survey which did not find any relationship over the course of 20 years [Vanderpump *et al.* 1995]. Recent meta-analysis has also reported an estimated 12% risk of development of SCH after hemithyroidectomy [Verloop *et al.* 2012].

Several studies have found an increased risk of thyroid cancer with rising TSH levels even within the normal range [Boelaert, 2009; Haymart *et al.* 2009; Fiore and Vitti, 2012] which is age independent; high TSH was also associated with advanced tumour stage [Kim *et al.* 2011]. A recent large, cross-sectional study revealed that normalisation of TSH by levothyroxine replacement in patients with nodular goitre resulted in a reduced risk of cancer [Fiore *et al.* 2010].

Based on these findings, recent ETA guidelines have suggested that SCH and even serum TSH variation within the normal range is associated with thyroid cancer development and progression. It has also suggested the logical conclusion is that treatment of nodular goitre with levothyroxine may protect against thyroid carcinoma development [Pearce *et al.* 2013].

Mild SCH and pregnancy

Gestational diabetes (GD)

It has been suggested that the risk of GD increases with increasing TSH levels [Tudela *et al.* 2012; Lazarus *et al.* 2014] (see Table 3 for trimester-specific TSH range). In one of the studies, a four-fold increase in the risk of GD was observed associated with subsequent increased risk of low birth weight neonates [Karakosta *et al.* 2012]. A recent meta-analysis revealed a 50% increase in the risk of GD in pregnant females with SCH compared with euthyroid population [Toulis *et al.* 2014].

Gestational hypertension and pre-eclampsia

Current data have shown that pregnant females with mild elevation of TSH have increased risk of gestational hypertension (GH) and pre-eclampsia. A recent systematic review revealed increased risk of pre-eclampsia in females with SCH compared with euthyroid females [van den Boogaard *et al.* 2011]. These findings were subsequently confirmed by another prospective population-based study [Wilson *et al.* 2012].

Preterm delivery, pregnancy loss and other complications

Current evidence indicated that even mildly raised TSH was associated with increased risk of miscarriage and foetal death [Ashoor *et al.* 2010; Lazarus *et al.* 2014]. Studies have shown that risk of miscarriage and foetal death increased by up to 60% for every doubling in TSH level and in females with mean TSH >6 mIU/l [Allan *et al.*

2000; Benhadi *et al.* 2009]. Another study found an increased incidence of foetal loss even when TSH was between 2.5 and 5.0 mIU/l in the first trimester compared with those who had TSH <2.5 mIU/l, suggesting that the TSH upper limit of normal should be 2.5 mIU/l in first trimester [Negro *et al.* 2010].

Studies have also shown an increased risk of premature delivery in patients with even mildly raised TSH [Casey *et al.* 2005; Su *et al.* 2011], which was further increased if positive for anti-TPO antibodies [Korevaar *et al.* 2013]. The data related to increased risk of other complications such as abruptio placentae, admission to neonatal intensive care unit, low birth weight and perinatal mortality are conflicting [Cleary-Goldman *et al.* 2008; Negro *et al.* 2010; Karakosta *et al.* 2012], but no increase in respiratory distress syndrome and congenital malformations have been observed [Casey *et al.* 2005; Cleary-Goldman *et al.* 2008; Negro *et al.* 2010].

Children born to mothers with SCH

The evidence related to association between impaired neuropsychological development and SCH in pregnancy is conflicting and insufficient [Lazarus *et al.* 2014]. Two Chinese studies found mildly elevated TSH in early pregnancy was associated with poor intellectual and motor development in children [Li *et al.* 2010; Su *et al.* 2011]. In contrast, several recent studies have not found any association between mildly raised TSH in early pregnancy and neuropsychological development in their offspring [Henrichs *et al.* 2010; Behrooz *et al.* 2011; Julvez *et al.* 2013].

Effects of levothyroxine treatment of SCH in pregnancy

There are only a few studies that have investigated the beneficial effects of treating SCH (TSH >2.5 mIU/l) in early pregnancy and revealed that levothyroxine treatment was associated with lower rate of adverse outcomes in both mother and foetus including reduction in miscarriage [Negro *et al.* 2010; Lepoutre *et al.* 2012]. Currently there is only one RCT which has assessed the effects of levothyroxine treatment on offspring intelligence quotient (IQ) and found no difference in cognitive function at the age of 3 years in children of women having mild-SCH who were treated during pregnancy compared with women who were not treated [Lazarus *et al.* 2012]. Similarly, one recently published trial has also found no long-term benefits of levothyroxine treatment on motor or mental development in children [Marchal *et al.* 2014].

The current guidelines suggest treating SCH with levothyroxine before conception and during gestation with the aim of keeping TSH within trimester-specific reference range [Lazarus *et al.* 2014]. There is no evidence available currently to support the beneficial effect of levothyroxine on the cognitive development of children in relation to maternal SCH, but there is an ongoing large-scale prospective RCT in the USA looking at the effects of thyroxine on the intellectual function of children at 5 years of age in women diagnosed with SCH in early pregnancy [ClinicalTrials.gov identifier: NCT00388297].

How to manage SCH?

It has been suggested in a recent Cochrane systematic review that thyroxine treatment in patients with SCH improved cardiovascular risk in terms of reducing serum cholesterol and improved cardiac function. But due to insufficient data, no clear recommendations could be stated and it was suggested that the decision either to treat or not should be on an individual basis [Villar *et al.* 2007] and by taking into account the factors listed in Table 2.

If the decision has been made not to treat patients with mild-SCH, then thyroid function tests

Table 2. Factors favouring levothyroxine treatment in patients having mild-SCH (4.5–10 mIU/l).

- Degree of TSH raised (2 TSH levels >8 mIU/l)×
- Progressive TSH increase
- Presence of goitre
- Presence of antithyroid antibodies
- Therapeutic trial for clinical symptoms
- Patient preference
- Young age of the patient
- Cardiovascular risk factors or prevalent CHD
- Smoking
- Dyslipidaemia
- Bipolar disorder, depression
- Pregnancy or intention of pregnancy
- Infertility, ovulatory dysfunction
- Childhood and adolescence

Adapted from: Baumgartner *et al.* [2014]; Fatourechi [2009]; Lazarus *et al.* [2014]; Pearce *et al.* [2013].
CHD, cardiovascular disease; mIU, SCH, subclinical hypothyroidism; TSH, thyroid stimulating hormone.

Table 3. Trimester-specific TSH reference ranges in different populations.

Population	TSH reference range (mIU/l)		
	1st trimester	2nd trimester	3rd trimester
USA	0.1–2.5	0.2–3.0	0.3–3.0
Chinese	0.03–4.51	0.05–4.50	0.47–4.54
Indian	0.6–5.0	0.44–5.78	0.74–5.7
Mixed (Dutch, Turkish, Moroccan, Surinamese)	0.06–4.51	Not mentioned	Not mentioned

Adapted from: De Groot *et al.* [2012]; Korevaar *et al.* [2013]; Li *et al.* [2014]; Marwaha *et al.* [2008]; Negro and Stagnaro-Green [2014]; Stagnaro-Green *et al.* [2011]; Yan *et al.* [2011].
mIU, milli-international unit; TSH, thyroid stimulating hormone.

(TFTs) should be rechecked along with anti-TPO antibodies within 8–12 weeks because thyroid function may normalize in 6–35% of patients [Surks *et al.* 2004; Karmisholt *et al.* 2011]. If TFTs become normalized, then there is no need to do further tests especially if the patients are asymptomatic, have no goitre and anti-TPO antibodies are not positive. But if SCH is persistent then TFTs should be tested every 6 months for the first 2 years and then annually thereafter [Pearce *et al.* 2013].

Oral levothyroxine is the treatment of choice if the decision to treat SCH has been made. Current evidence does not suggest use of either liothyronine (T3) or combined levothyroxine/liothyronine treatment for SCH [Grozinsky-Glasberg *et al.* 2006; Pearce *et al.* 2013]. The ETA guidelines recommend a weight-adjusted starting dose of 1.5 μg/kg daily (e.g. 100 or 125 μg/daily for a man, 75 or 100 μg for woman) for patients without cardiac disease and 25–50 μg daily for patients having heart problems and in the elderly [Pearce *et al.* 2013]. The serum TSH should be rechecked 2–3 months after starting levothyroxine with the aim of keeping TSH in the lower half of recommended range (0.4–2.5 mIU/l), though a higher reference range (1.0–5.0 mIU/l) is acceptable in elderly patients (>70 years) [Biondi and Cooper, 2008].

Patients having mild-TSH (<10 mIU/l) who are started on treatment mainly due to symptoms should be reviewed 3–4 months after normalization of TSH and treatment should be stopped if there is no improvement in symptoms [Pearce *et al.* 2013].

For pregnant women with TSH above the trimester specific TSH values (Table 3) or for women who wish to become pregnant with TSH >2.5 mIU/l, initiation of treatment is recommended [Surks *et al.* 2004; Baumgartner *et al.* 2014]. The treatment of choice is oral levothyroxine; a starting dose of 1.20 μg/kg/day has been advised in newly diagnosed patients while an increase in dose of 25–50% has been advised if diagnosed before conception [Abalovich *et al.* 2013; Lazarus *et al.* 2014]. TSH levels should be checked every 4–6 weeks during the first trimester and at least once in the subsequent trimesters while on levothyroxine treatment [Yassa *et al.* 2010] and dose should be adjusted to keep TSH within the trimester-specific reference range (Table 3).

The risks of overtreatment have been reported in 14–21% of patients; they include nervousness, palpitations, ischemic heart disease, atrial fibrillation, heart failure and decreased bone mineral density with subsequent increased risk of fracture [Helfand *et al.* 2004; Flynn *et al.* 2010; Baumgartner *et al.* 2014].

Conclusion

Mild-SCH is still a topic of debate regarding the risks associated and whether treatment is beneficial in these patients or not. The balance of risk and benefit is influenced by the degree of TSH elevation. Patients with TSH levels between 3.0 and 5.0 mIU/l are unlikely to show a clinically significant abnormality and levothyroxine replacement at these levels may or may not provide a benefit. The recommendations related to the management of SCH patients with TSH of 5.0–10.0 mIU/l suggest making a decision by taking into account the associated risk factors and comorbid conditions (Table 2). Further large RCTs to solve these controversies have been suggested and a few are underway.

Funding

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

Abalovich, M., Vazquez, A., Alcaraz, G., Kitaigrodsky, A., Szuman, G., Calabrese, C. *et al.* (2013) Adequate levothyroxine doses for the treatment of hypothyroidism newly discovered during pregnancy. *Thyroid* 23: 1479–1483.

Aghili, R., Khamseh, M., Malek, M., Hadian, A., Baradaran, H., Najafi, L. *et al.* (2012) Changes of subtests of Wechsler Memory Scale and cognitive function in subjects with subclinical hypothyroidism following treatment with levothyroxine. *Arch Med Sci* 8: 1096–1101.

Allan, W., Haddow, J., Palomaki, G., Williams, J., Mitchell, M., Hermos, R. *et al.* (2000) Maternal thyroid deficiency and pregnancy complications: implications for population screening. *J Med Screen* 7: 127–130.

Andersen, M., Olsen, A., Madsen, J., Faber, J., Torp-Pedersen, C., Gislason, G. *et al.* (2015) Levothyroxine substitution in patients with subclinical hypothyroidism and the risk of myocardial infarction and mortality. *PLoS One* 10: e0129793.

Ashoor, G., Maiz, N., Rotas, M., Jawdat, F. and Nicolaides, K. (2010) Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. *Thyroid* 20: 989–993.

Baldini, I., Vita, A., Mauri, M., Amodei, V., Carrisi, M., Bravin, S. *et al.* (1997) Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry* 21: 925–935.

Baumgartner, C., Blum, M. and Rodondi, N. (2014) Subclinical hypothyroidism: summary of evidence in 2014. *Swiss Med Wkly* 144: w14058.

Behrooz, H., Tohidi, M., Mehrabi, Y., Behrooz, E., Tehranidoost, M. and Azizi, F. (2011) Subclinical hypothyroidism in pregnancy: intellectual development of offspring. *Thyroid* 21: 1143–1147.

Benhadi, N., Wiersinga, W., Reitsma, J., Vrijkotte, T. and Bonsel, G. (2009) Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 160: 985–991.

Bindels, A., Westendorp, R., Frolich, M., Seidell, J., Blokstra, A. and Smelt, A. (1999) The prevalence of subclinical hypothyroidism at different total plasma cholesterol levels in middle aged men and women: a need for case-finding? *Clin Endocrinol* 50: 217–220.

Biondi, B. (2007) Cardiovascular effects of mild hypothyroidism. *Thyroid* 17: 625–630.

Biondi, B. and Cooper, D. (2008) The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29: 76–131.

Boekholdt, S., Titan, S., Wiersinga, W., Chatterjee, K., Basart, D., Luben, R. *et al.* (2010) Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk Prospective Population Study. *Clin Endocrinol* 72: 404–410.

Boelaert, K. (2009) The association between serum TSH concentration and thyroid cancer. *Endocr Relat Cancer* 16: 1065–1072.

Brennan, M., Powell, C., Kaufman, K., Sun, P., Bahn, R. and Nair, K. (2006) The impact of overt and subclinical hyperthyroidism on skeletal muscle. *Thyroid* 16: 375–380.

Canaris, G., Manowitz, N., Mayor, G. and Ridgway, E. (2000) The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med* 160: 526–534.

Caraccio, N., Ferrannini, E. and Monzani, F. (2002) Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab* 87: 1533–1538.

Casey, B., Dashe, J., Wells, C., Mcintire, D., Byrd, W., Leveno, K. *et al.* (2005) Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 105: 239–245.

Chikunguwo, S., Brethauer, S., Nirujogi, V., Pitt, T., Udomsawaengsup, S., Chand, B. *et al.* (2007) Influence of obesity and surgical weight loss on thyroid hormone levels. *Surg Obes Relat Dis* 3: 631–635; discussion 635–636.

Cleary-Goldman, J., Malone, F., Lambert-Messerlian, G., Sullivan, L., Canick, J., Porter, T. *et al.* (2008) Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 112: 85–92.

Correia, N., Mullally, S., Cooke, G., Tun, T., Phelan, N., Feeney, J. *et al.* (2009) Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocrinol Metab* 94: 3789–3797.

Dall'asta, C., Paganelli, M., Morabito, A., Vedani, P., Barbieri, M., Paolisso, G. *et al.* (2010) Weight loss through gastric banding: effects on TSH and thyroid hormones in obese subjects with normal thyroid function. *Obesity* 18: 854–857.

Danese, M., Ladenson, P., Meinert, C. and Powe, N. (2000) Clinical Review 115: Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 85: 2993–3001.

De Groot, L., Abalovich, M., Alexander, E., Amino, N., Barbour, L., Cobin, R. *et al.* (2012) Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 97: 2543–2565.

De Moura Souza, A. and Sichieri, R. (2011) Association between serum TSH concentration within the normal range and adiposity. *Eur J Endocrinol* 165: 11–15.

Del Ser Quijano, T., Delgado, C., Martinez Espinosa, S. and Vazquez, C. (2000) [Cognitive deficiency in mild hypothyroidism]. *Neurologia* 15: 193–198.

Diez, J. and Iglesias, P. (2004) Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab* 89: 4890–4897.

Fatourechi, V. (2009) subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc* 84: 65–71.

Fiore, E., Rago, T., Provenzale, M., Scutari, M., Ugolini, C., Basolo, F. *et al.* (2010) L-Thyroxine-treated patients with nodular goiter have lower serum TSH and lower frequency of papillary thyroid cancer: results of a cross-sectional study on 27,914 Patients. *Endocr Relat Cancer* 17: 231–239.

Fiore, E. and Vitti, P. (2012) Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. *J Clin Endocrinol Metab* 97: 1134–1145.

Flynn, R., Bonellie, S., Jung, R., Macdonald, T., Morris, A. and Leese, G. (2010) Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab* 95: 186–193.

Fox, C., Pencina, M., D'Agostino, R., Murabito, J., Seely, E., Pearce, E. *et al.* (2008) Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med* 168: 587–592.

Grozinsky-Glasberg, S., Fraser, A., Nahshoni, E., Weizman, A. and Leibovici, L. (2006) Thyroxine-triiodothyronine combination therapy *versus* thyroxine monotherapy for clinical hypothyroidism: meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 91: 2592–2599.

Gussekloo, J., Van Exel, E., De Craen, A., Meinders, A., Frolich, M. and Westendorp, R. (2004) Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 292: 2591–2599.

Hak, A., Pols, H., Visser, T., Drexhage, H., Hofman, A. and Witteman, J. (2000) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 132: 270–278.

Haymart, M., Glinberg, S., Liu, J., Sippel, R., Jaume, J. and Chen, H. (2009) Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. *Clin Endocrinol)* 71: 434–439.

Helfand, M. and the US Preventative Services Task Force (2004) Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 140: 128–141.

Henrichs, J., Bongers-Schokking, J., Schenk, J., Ghassabian, A., Schmidt, H., Visser, T. *et al.* (2010) maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R study. *J Clin Endocrinol Metab* 95: 4227–4234.

Joffe, R., Pearce, E., Hennessey, J., Ryan, J. and Stern, R. (2013) Subclinical hypothyroidism, mood, and cognition in older adults: a review. *Int J Geriatr Psychiatry* 28: 111–118.

Jorde, R., Waterloo, K., Storhaug, H., Nyrnes, A., Sundsfjord, J. and Jenssen, T. (2006) Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab* 91: 145–153.

Julvez, J., Alvarez-Pedrerol, M., Rebagliato, M., Murcia, M., Forns, J., Garcia-Esteban, R. *et al.* (2013) Thyroxine levels during pregnancy in healthy women and early child neurodevelopment. *Epidemiology* 24: 150–157.

Kahaly, G. (2012) Polyglandular autoimmune syndrome type II. *Presse Med* 41: e663–e670.

Karakosta, P., Alegakis, D., Georgiou, V., Roumeliotaki, T., Fthenou, E., Vassilaki, M. *et al.* (2012) Thyroid dysfunction and autoantibodies in early pregnancy are associated with increased risk of gestational diabetes and adverse birth outcomes. *J Clin Endocrinol Metab* 97: 4464–4472.

Karmisholt, J., Andersen, S. and Laurberg, P. (2011) Variation in thyroid function in subclinical hypothyroidism: importance of clinical follow-up and therapy. *Eur J Endocrinol* 164: 317–323.

Kim, S., Lee, B., Lee, J., Song, S., Kim, B., Son, S. *et al.* (2011) Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in

Korean patients: a single-center experience. *Endocrine* 39: 259–265.

Kitahara, C., Platz, E., Ladenson, P., Mondul, A., Menke, A. and Berrington De Gonzalez, A. (2012) Body fatness and markers of thyroid function among U.S. men and women. *PLoS One* 7: e34979.

Kong, W., Sheikh, M., Lumb, P., Naoumova, R., Freedman, D., Crook, M. *et al.* (2002) A 6-Month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med* 112: 348–354.

Korevaar, T., Medici, M., De Rijke, Y., Visser, W., De Muinck Keizer-Schrama, S., Jaddoe, V. *et al.* (2013a) Ethnic differences in maternal thyroid parameters during pregnancy: the Generation R study. *J Clin Endocrinol Metab* 98: 3678–3686.

Korevaar, T., Schalekamp-Timmermans, S., De Rijke, Y., Visser, W., Visser, W., De Muinck Keizer-Schrama, S. *et al.* (2013b) Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the Generation R study. *J Clin Endocrinol Metab* 98: 4382–4390.

Kvetny, J., Heldgaard, P., Bladbjerg, E. and Gram, J. (2004) Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol* 61: 232–238.

Lazarus, J., Bestwick, J., Channon, S., Paradice, R., Maina, A., Rees, R. *et al.* (2012) Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 366: 493–501.

Lazarus, J., Brown, R., Daumerie, C., Hubalewska-Dydejczyk, A., Negro, R. and Vaidya, B. (2014) 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 3: 76–94.

Lee, J., Buzkova, P., Fink, H., Vu, J., Carbone, L., Chen, Z. *et al.* (2010) Subclinical thyroid dysfunction and incident hip fracture in older adults. *Arch Intern Med* 170: 1876–1883.

Lepoutre, T., Debieve, F., Gruson, D. and Daumerie, C. (2012) Reduction of miscarriages through universal screening and treatment of thyroid autoimmune diseases. *Gynecol Obstet Invest* 74: 265–273.

Li, C., Shan, Z., Mao, J., Wang, W., Xie, X., Zhou, W. *et al.* (2014) Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab* 99: 73–79.

Li, Y., Shan, Z., Teng, W., Yu, X., Li, Y., Fan, C. *et al.* (2010) Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. *Clin Endocrinol* 72: 825–829.

Liu, D., Jiang, F., Shan, Z., Wang, B., Wang, J., Lai, Y. *et al.* (2010) A cross-sectional survey of relationship between serum TSH level and blood pressure. *J Hum Hypertens* 24: 134–138.

Mainenti, M., Vigario, P., Teixeira, P., Maia, M., Oliveira, F. and Vaisman, M. (2009) Effect of levothyroxine replacement on exercise performance in subclinical hypothyroidism. *J Endocrinol Invest* 32: 470–473.

Marchal, J., Maurice-Stam, H., Ikelaar, N., Klouwer, F., Verhorstert, K., Witteveen, M. *et al.* (2014) Effects of early thyroxine treatment on development and growth at age 10.7 years: follow-up of a randomized placebo-controlled trial in children with Down's Syndrome. *J Clin Endocrinol Metab* 99: E2722–2729.

Marwaha, R., Chopra, S., Gopalakrishnan, S., Sharma, B., Kanwar, R., Sastry, A. *et al.* (2008) Establishment of reference range for thyroid hormones in normal pregnant Indian women. *BJOG* 115: 602–606.

Monzani, A., Prodam, F., Rapa, A., Moia, S., Agarla, V., Bellone, S. *et al.* (2013) Endocrine Disorders in childhood and adolescence. Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. *Eur J Endocrinol* 168: R1–R11.

Monzani, F., Caraccio, N., Kozakowa, M., Dardano, A., Vittone, F., Virdis, A. *et al.* (2004) Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. *J Clin Endocrinol Metab* 89: 2099–2106.

Monzani, F., Di Bello, V., Caraccio, N., Bertini, A., Giorgi, D., Giusti, C. *et al.* (2001) Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab* 86: 1110–1115.

Mooijaart, S. (2012) Subclinical thyroid disorders. *Lancet* 380: 335; author reply 336–337.

Negro, R., Schwartz, A., Gismondi, R., Tinelli, A., Mangieri, T. and Stagnaro-Green, A. (2010a) Increased pregnancy loss rate in thyroid antibody negative women with TSH Levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab* 95: E44–E48.

Negro, R., Schwartz, A., Gismondi, R., Tinelli, A., Mangieri, T. and Stagnaro-Green, A. (2010b) Universal screening *versus* case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 95: 1699–1707.

Negro, R. and Stagnaro-Green, A. (2014) Diagnosis and management of subclinical hypothyroidism in pregnancy. *BMJ* 349: g4929.

Nyrnes, A., Jorde, R. and Sundsfjord, J. (2006) Serum TSH is positively associated with BMI. *Int J Obes* 30: 100–105.

Ochs, N., Auer, R., Bauer, D., Nanchen, D., Gussekloo, J., Cornuz, J. *et al.* (2008) Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med* 148: 832–845.

Parle, J., Roberts, L., Wilson, S., Pattison, H., Roalfe, A., Haque, M. *et al.* (2010) A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham elderly thyroid study. *J Clin Endocrinol Metab* 95: 3623–3632.

Parsaik, A., Singh, B., Roberts, R., Pankratz, S., Edwards, K., Geda, Y. *et al.* (2014) Hypothyroidism and risk of mild cognitive impairment in elderly persons: a population-based study. *JAMA Neurol* 71: 201–207.

Pearce, S., Brabant, G., Duntas, L., Monzani, F., Peeters, R., Razvi, S. *et al.* (2013) 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2: 215–228.

Perros, P., Mccrimmon, R., Shaw, G. and Frier, B. (1995) Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabet Med* 12: 622–627.

Razvi, S., Ingoe, L., Keeka, G., Oates, C., Mcmillan, C. and Weaver, J. (2007) The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 92: 1715–1723.

Razvi, S., Shakoor, A., Vanderpump, M., Weaver, J. and Pearce, S. (2008) the influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *J Clin Endocrinol Metab* 93: 2998–3007.

Razvi, S., Weaver, J., Butler, T. and Pearce, S. (2012) Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. *Arch Intern Med* 172: 811–817.

Reuters, V., Teixeira, P., Vigario, P., Almeida, C., Buescu, A., Ferreira, M. *et al.* (2009) Functional capacity and muscular abnormalities in subclinical hypothyroidism. *Am J Med Sci* 338: 259–263.

Rodondi, N., Aujesky, D., Vittinghoff, E., Cornuz, J. and Bauer, D. (2006) Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. *Am J Med* 119: 541–551.

Rodondi, N. and Bauer, D. (2013) Subclinical hypothyroidism and cardiovascular risk: how to end the controversy. *J Clin Endocrinol Metab* 98: 2267–2269.

Rodondi, N., Den Elzen, W., Bauer, D., Cappola, A., Razvi, S., Walsh, J. *et al.* (2010) Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 304: 1365–1374.

Rozing, M., Houwing-Duistermaat, J., Slagboom, P., Beekman, M., Frolich, M., De Craen, A. *et al.* (2010) familial longevity is associated with decreased thyroid function. *J Clin Endocrinol Metab* 95: 4979–4984.

Simonsick, E., Newman, A., Ferrucci, L., Satterfield, S., Harris, T., Rodondi, N. *et al.* (2009) Subclinical hypothyroidism and functional mobility in older adults. *Arch Intern Med* 169: 2011–2017.

Skarulis, M., Celi, F., Mueller, E., Zemskova, M., Malek, R., Hugendubler, L. *et al.* (2010) Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. *J Clin Endocrinol Metab* 95: 256–262.

Somwaru, L., Rariy, C., Arnold, A. and Cappola, A. (2012) the natural history of subclinical hypothyroidism in the elderly: the Cardiovascular Health Study. *J Clin Endocrinol Metab* 97: 1962–1969.

Spencer, C., Hollowell, J., Kazarosyan, M. and Braverman, L. (2007) National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. *J Clin Endocrinol Metab* 92: 4236–4240.

Stagnaro-Green, A., Abalovich, M., Alexander, E., Azizi, F., Mestman, J., Negro, R. *et al.* (2011) Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 21: 1081–1125.

Stanicka, S., Vondra, K., Pelikanova, T., Vlcek, P., Hill, M. and Zamrazil, V. (2005) Insulin sensitivity and counter-regulatory hormones in hypothyroidism and during thyroid hormone replacement therapy. *Clin Chem Lab Med* 43: 715–720.

Su, P., Huang, K., Hao, J., Xu, Y., Yan, S., Li, T. *et al.* (2011) Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab* 96: 3234–3241.

Surks, M. and Hollowell, J. (2007) Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 92: 4575–4582.

Surks, M., Ortiz, E., Daniels, G., Sawin, C., Col, N., Cobin, R. *et al.* (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291: 228–238.

Svare, A., Nilsen, T., Asvold, B., Forsmo, S., Schei, B., Bjoro, T. *et al.* (2013) Does thyroid function influence fracture risk? Prospective data from the Hunt2 study, Norway. *Eur J Endocrinol* 169: 845–852.

Toulis, K., Stagnaro-Green, A. and Negro, R. (2014) Maternal subclinical hypothyroidsm and gestational diabetes mellitus: a meta-analysis. *Endocr Pract* 20: 703–714.

Triolo, T., Armstrong, T., Mcfann, K., Yu, L., Rewers, M., Klingensmith, G. *et al.* (2011) Additional autoimmune disease found in 33% of patients at type 1 diabetes onset. *Diabetes Care* 34: 1211–1213.

Tudela, C., Casey, B., Mcintire, D. and Cunningham, F. (2012) Relationship of subclinical thyroid disease to the incidence of gestational diabetes. *Obstet Gynecol* 119: 983–988.

Van den Boogaard, E., Vissenberg, R., Land, J., Van Wely, M., van der Post, J., Goddijn, M. *et al.* (2011) Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. *Hum Reprod Update* 17: 605–619.

Vanderpump, M., Tunbridge, W., French, J., Appleton, D., Bates, D., Clark, F. *et al.* (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham survey. *Clin Endocrinol* 43: 55–68.

Verloop, H., Louwerens, M., Schoones, J., Kievit, J., Smit, J. and Dekkers, O. (2012) Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. *J Clin Endocrinol Metab* 97: 2243–2255.

Villar, H., Saconato, H., Valente, O. and Atallah, A. (2007) Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*: CD003419.

Virgini, V., Wijsman, L., Rodondi, N., Bauer, D., Kearney, P., Gussekloo, J. *et al.* (2014) Subclinical thyroid dysfunction and functional capacity among elderly. *Thyroid* 24: 208–214.

Walsh, J., Bremner, A., Bulsara, M., O'Leary, P., Leedman, P., Feddema, P. *et al.* (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med* 165: 2467–2472.

Wilson, K., Casey, B., McIntire, D., Halvorson, L. and Cunningham, F. (2012) subclinical thyroid disease and the incidence of hypertension in pregnancy. *Obstet Gynecol* 119: 315–320.

Yan, Y., Dong, Z., Dong, L., Wang, F., Yang, X., Jin, X. *et al.* (2011) Trimester- and method-specific reference intervals for thyroid tests in pregnant Chinese women: methodology, euthyroid definition and iodine status can influence the setting of reference intervals. *Clin Endocrinol* 74: 262–269.

Yassa, L., Marqusee, E., Fawcett, R. and Alexander, E. (2010) Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab* 95: 3234–3241.

Visit SAGE journals online
http://tae.sagepub.com

SAGE journals