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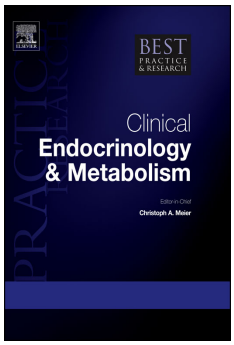

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Indications for Treatment of Subclinical Hypothyroidism and Isolated Hypothyroxinaemia in Pregnancy

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Abstract

Thyroid hormones are essential for maintaining a pregnancy and optimal fetal neurological development. Pregnancy places additional demands on the thyroid axis and around 5% of women who have their thyroid function checked during gestation will have borderline low thyroid function (subclinical hypothyroidism or isolated hypothyroxinemia) identified. These borderline low thyroid states are associated with adverse obstetric and offspring outcomes. Whilst it is well established that overt hypothyroidism requires treatment with levothyroxine, it is less clear whether there is any benefit of treating borderline low thyroid states. This review summarizes the potential indications for treatment of subclinical hypothyroidism and isolated hypothyroxinemia.

Practice Points

- Where possible, laboratory reference ranges should be reflective of the local population.
- Women established on levothyroxine will often have borderline thyroid function in pregnancy and need education ideally prenatally to optimize outcomes in the offspring.
- SCH is associated most strongly with adverse obstetric outcomes, whereas IH is associated with adverse neurological development in offspring.
- SCH in particular in those with TPO antibody positivity may need treatment.
- In IH the benefit of treatment is less clear.

Research agenda

- Trials of correcting borderline low thyroid function in early pregnancy are urgently needed with assessment of obstetric and offspring outcomes.

Introduction

Thyroid hormone is essential for maintaining pregnancy and for foetal development [1]. In fact the foetus is totally dependent from maternal thyroid hormones for the first half of pregnancy[2,3], therefore the negative impact of profound maternal hypothyroidism during gestation and the absolute indication to promptly treat this condition are well established[4-6]. Furthermore, critical neurological development occurs in early pregnancy and this is a key period of vulnerability with regard to foetal loss[1,7]. Appropriate supply of thyroid hormone during this delicate phase is therefore crucial.

It is well established that profound hypothyroidism during pregnancy can result in severe obstetric complications including foetal loss and prematurity as well as profound intellectual disability in the offspring. Clinically, thyroid function is assessed by measuring the pituitary hormone thyrotropin (TSH) and free thyroid hormone levels, free-triiodothyronine (FT3) and free-thyroxine (FT4).

More recently there has been a focus on the consequences of maternal borderline low thyroid function, subclinical hypothyroidism (SCH) and isolated hypothyroxinemia (IH). SCH is defined as a TSH level above the pregnancy reference range with a normal FT4 level, whereas IH as the presence of low FT4 with a normal TSH level. There is growing evidence that these borderline hypothyroid states during gestation are associated with adverse obstetric and offspring outcomes albeit to a lesser extent than that observed in overt disease. What is less clear are the benefits of treating SCH and IH in pregnancy. This is an important issue to address, as thyroid function is often measured in pregnancy and these are common biochemical abnormalities encountered. The aim of this review is to briefly summarize what is known regarding the epidemiology and adverse effects of SCH and IH and then focus on treatment considerations and highlight uncertainties.

The management of these borderline thyroid abnormalities in pregnancy are key in the debate as to the need for universal thyroid screening in pregnancy [8]. This review is timely as there has been a substantial increase in our knowledge of thyroid physiology in pregnancy and thyroid disorders are very common among women of child-bearing age [9]. We will however, first briefly review the pertinent changes in thyroid hormone axis and physiology over pregnancy and discuss key implications of thyroid function in pregnancy.

Thyroid hormone axis in pregnancy

It is increasingly well recognised that thyroid physiology undergoes profound, but reversible, changes during pregnancy, summarized in **Box 1**. Overall these lead to increased requirements of iodine, an essential component for thyroid hormone synthesis, and enhanced utilisation of thyroid hormones over pregnancy [1,10-12]. However there is a modest stimulatory effect of human chorionic gonadotrophin (hCG) on the thyroid which may offset this to an extent. Crucially, there is growing evidence that thyroid autoimmunity, especially positivity to autoantibodies to thyroid peroxidase (TPOAb) impairs the thyroidal response to hCG [13]

Thus the thyroid gland of women from iodine deficient areas and those affected with thyroid autoimmunity may be unable to adjust its economy to fulfil the additional pregnancy requirements [6]. The increased iodine requirements in pregnancy also mean that some countries who are just sufficient for the normal adult population have insufficient iodine status for pregnancy. In this regard, pregnancy contributes to bring to light some underlying iodine deficiencies. The UK and Russia are two notable countries that have inadequate iodine status for pregnant women and do not have universal salt iodisation [14].

Box 1 Summary of Physiologic changes in the thyroid axis in pregnancy

Provides Support

- ↑ **hCG levels** – stimulates the thyroid to produce thyroid hormone, resulting in ↑FT4 and ↓ TSH although this effect may be impaired in women positive for autoantibodies to thyroid peroxidase (TPOAb).

Provides Demand

- ↑ **thyroid binding globulin (TBG)** - ↑ total T4 and T3 concentration
- ↑ **deiodinase 3 (DIO3) activity from the placenta** - ↑T4 and T3 degradation
- ↑ **Renal iodine clearance** - ↑ iodine requirements with ↓ hormone production in iodine deficient areas
- ↑ **plasma volume** - ↑ T4 and T3 pool size
- **Fetal consumption of thyroid hormone**

Assessment of thyroid status in pregnancy

Outside of pregnancy the complex inverse association between TSH and FT4 renders TSH the more sensitive marker of thyroid status[15]. However thyroid function assessment in pregnancy using TSH concentration is more difficult due to the effect of hCG, therefore FT4 has greater importance in interpretation than in the general adult population. Current American Thyroid Association (ATA) guidance for thyroid assessment during gestation recommends the use of pregnancy specific reference ranges, which should be locally based where possible and trimester specific[6,16].

Thyroid hormones circulate for the near totality (>99%) bound to transport proteins such as thyroid binding globulin (TBG), transthyretin and albumin, at equilibrium with the free quote (FT4 and FT3) representing the active form of thyroid hormones [17]. Raised levels of oestrogen results in increased levels of TBG and this explains the presence of fluctuations in total T4 concentrations throughout gestation[12]. For this reason, FT4 and FT3 concentrations are preferred as only the biologically active form is analysed in these assays[12]. In addition, there is more robust evidence for the association between the free hormone levels (especially FT4) and adverse obstetric and offspring outcomes also supporting this mode of analysis[1,18,19]. Challenges with this method however, arise due to lower concentration of the analyte, risk of disequilibrium between the free and protein-bound hormone and the potential for interference from the much higher concentrations of the protein-bound hormone. Of note, the interference varies depending on the method used and stage of gestation[12]. Some experts are endorsing longitudinal trajectory calculations during gestation[20].

Gestational thyroid hypo function: epidemiology and significance

Maternal overt hypothyroidism (OH), characterised by elevated TSH and low maternal FT4, occurs in approximately 0.2-0.6% of pregnant women[21,22]. All endocrine and obstetric societies recommend its treatment[12]. SCH is much more common, but it is difficult to establish precise prevalence figures due to the different diagnostic criteria and cut-offs used across different countries, and subsequent versions of clinical guidelines [23]. SCH, which is defined as TSH above the pregnancy reference range and normal FT4, can occur in up to 18% of pregnancies depending on the precise definition and TSH cut-point used [1,6].

IH is now usually defined as a normal TSH with FT4 concentrations in the lower 2.5-5th percentile of local pregnancy-specific reference range [6]. There is large variation in the estimated prevalence during pregnancy and has been quoted as ranging from 1.3 to 23.9%[24] depending on FT4 cut-off, iodine sufficiency, gestational age, whether pregnancy-specific reference ranges have been used and indeed the definition used to identify those with IH (previous definitions included FT4 concentrations up to the 10th percentile).

IH was originally considered to be a pregnancy specific condition possibly arising due to mild iodine deficiency. However, this has been challenged as it occurs in iodine sufficient areas and does not typically resolve with iodine supplementation [25,26]. Several other factors have now been identified as potential risk factors for IH, summarised in **Box 2** [24,27-29]. This is important to recognise as these are all associated with negative pregnancy outcomes *per se* and therefore raises the possibility that some of the adverse associations observed with IH may be due to confounding. Interestingly thyroid autoimmunity does not appear to be a risk factor for IH [24].

Box 2 Potential causes of gestational IH

- Iodine deficiency
- Environmental pollutants (thiocyanates, polychlorinated biphenyls)
- Obesity
- Placental angiogenic factors (PlGF, sFlt1)
- Older maternal age
- Iron deficiency

Adverse outcomes associated with SCH and IH

OH and iodine deficiency occurring during gestation have a well-established profound negative impact on pregnancy and foetal/neonatal outcomes [30-32]. Among offspring's effects particular emphasis has been placed on the impaired neurodevelopment caused by such conditions, that in its more severe form is known as "cretinism", characterised by an intelligence quotient (IQ) of 40 or less [33]. In addition to detrimental effects of child's neuropsychological development, especially

IQ reduction [2], untreated gestational OH has been also associated with premature delivery, low-birth weight, miscarriage and pre-eclampsia, [34].

Similarly, numerous observational studies and meta-analysis have demonstrated the association between gestational SCH with both pregnancy (pre-eclampsia, miscarriage, placental abruption) and offspring (premature delivery, neonatal death) negative outcomes [23,35,36], summarized in **Table 1**, but not adverse offspring neurobehavioral outcomes, in sharp contrast with OH [18,37,38].

Gestational IH is predominantly associated with offspring adverse neurodevelopment outcomes, expressed as various parameters such as mental, cognitive, language and motor/psychomotor delays [38-41]. In addition, adverse neurobehavioral outcomes have also been described in gestational IH, including attention deficit and hyperactivity disorder (AHDH) [42,43], autism spectrum disorder [44], schizophrenia [45], slower reaction times [46], suboptimal school performances [47], and lower grey matter and cortex volumes [18]. Gestational IH has also been found to be associated with premature birth[39]. There is a substantial lack of studies investigating pregnancy outcomes in women with gestational IH [6]. Outcomes associated with gestational IH have been summarized in **Table 2**.

Taken together it is intriguing that the adverse outcomes of SCH and IH appear to be distinct. SCH is associated more clearly with adverse obstetric outcomes whereas IH is more robustly associated with adverse neurocognitive and behaviour findings in offspring. This may reflect differing foetal exposure to T4, as in IH the foetus will be exposed to lower T4 levels than in SCH. It also may reflect differences in aetiology as TPOAb positive women are more likely to have SCH whereas IH is more commonly linked with other features, previously summarised in **Box 2**. Mechanistically, SCH seems to provide an adverse metabolic environment that jeopardises pregnancy outcomes, meanwhile IH particularly impairs FT4 availability and neuronal migration processes dependent on it[48,49]. Therefore, SCH and IH will determine different epigenetic pathways.

In addition it is intriguing that thyroid autoimmunity is also associated with adverse pregnancy and offspring outcomes [1]. This can be a consequence of TPOAb positivity being often associated with raised TSH and reduced FT4 levels, and therefore a higher risk of both SCH and OH, 8 and 26 fold respectively [50]. However, TPOAb positivity *per se* has a negative impact independent of thyroid function on several pregnancy outcomes, such as pregnancy loss and premature delivery [39,51,52]. Furthermore, the combination of SCH and TPOAb positivity synergistically triggers higher risks of several negative pregnancy outcomes including gestational diabetes mellitus, premature delivery and pregnancy loss [1,39,53-55]. TPOAb positivity and negative pregnancy outcomes could be spuriously associated due to a common underlying autoimmune condition, however the evidence that some negative effects of TPOAb positivity are mitigated by the administration of levothyroxine treatment suggests that one of the main mechanisms may be indeed the alteration of normal thyroid function [56-58]. However the large TABLET trial[59] did not find any benefit of levothyroxine on live births in euthyroid women with TPOAb positivity. An additional mechanism is suggested by the evidence that TPOAb positive women have

an impaired physiological response to early-pregnancy hCG peak, leading to reduced availability of thyroid hormone levels [13].

Evidence of the benefits of screening for and treating borderline low thyroid function in pregnancy

To date, there have been three large randomized controlled trials investigating the effects of screening and treating borderline low thyroid function (including SCH and IH) in pregnancy and all failed to demonstrate clear treatment benefits in terms of both pregnancy and offspring outcomes [60-64]. These are the controlled antenatal thyroid screening (CATS) study [60] a study by Casey *et al.* [65], and a recent study by Nazarpour *et al.* [62], summarized in **Table 3**.

In particular, the controlled antenatal thyroid screening (CATS) study [60] and the Casey study [61] found no impact of levothyroxine treatment for suboptimal gestational thyroid function in terms of offspring neurodevelopment, mainly expressed as IQ. A potential reason for negative findings might be relatively late initiation of treatment, especially for Casey study (Casey: 16.6 weeks of gestation, CATS: 12.3 weeks of gestation), thereby missing the treatment window as critical neurological development occurred before treatment initiation. Another reason can be a too early age of IQ assessment, especially for CATS study (age 3) [12,60]. However, a recent follow-on CATS study (CATS-II) confirmed no apparent levothyroxine benefits in terms of IQ at age 9 [64].

Similarly when evaluating the pregnancy outcomes both Casey study [61] and Nazarpour study [62], as well as a meta-analysis including both [63], failed to observe significant benefits from levothyroxine treatment in terms of placental abruption, preterm delivery <37 weeks gestation, gestational age at delivery, neonatal intensive care admission and head circumference. In contrast, a more recent meta-analysis including the majority of CATS cohort using data linkage identified a reduced risk of pregnancy loss[66], in accordance with previous observations also identifying a reduced risk of pre-term delivery [56].

Current proposed guidelines for the treatment of SCH and IH

Initially, international guidelines recommended to keep TSH levels below 2.5 mU/L and 3.0 mU/L in the first and second/third trimesters, respectively [4,5]. However the challenge in defining universal trimester-specific reference ranges due to geographical differences led to more flexible recent recommendations, aiming to keep TSH levels during the first trimester in the lower half of the trimester-specific reference range, with a gradual return to non-pregnant reference ranges during the remaining two trimesters [6]. The parallel measurement of FT4 (not TT4) is also recommended; considering the even more significant geographical and methodological differences compared with TSH assay, the general recommendation is to interpret gestational FT4 levels using local pregnancy-specific reference ranges [6].

Such recommendations are easy to follow in cases of patients already on levothyroxine treatment before pregnancy or diagnosed with gestational OH. It is more challenging to provide clear guidelines about milder forms such as SCH and IH

diagnosed during pregnancy, due to the still weak evidence of treatment benefits in these conditions.

With regard to gestational IH there is disparity between current thyroid association guidelines. The European Thyroid Association (ETA) guidance indicates that treatment of IH can be considered in the first trimester [67] although the ATA guidance does not recommend any specific treatment for IH [6] and is more in favour of treating SCH. Crucially this guidance provides latitude for clinicians and includes the evaluation of TPOAb positivity.

The measurement of TPOAb should always be performed in women with SCH and IH, since TPOAb positivity is an independent risk factor for pregnancy outcomes [39,51,52] also acting in synergy with SCH [1,39,53-55]. If TPOAb positivity is associated with TSH levels 2.5-10.0 mU/L, commencing treatment with low doses of levothyroxine (25-50 μg daily) is usually recommended, considering the potential benefits and the minimal risk [6]. There is no current indication to start levothyroxine treatment in TPOAb positive women with TSH concentrations within the normal (pregnancy-specific) reference range. This has been highlighted by the recent TABLET trial[59] where levothyroxine in euthyroid women with thyroid peroxidase antibodies did not result in a higher rate of live births than placebo. Another trial "T4Lifetrial" (the Netherlands) is ongoing. However, levothyroxine treatment was found to reduce the rate of pregnancy loss in two independent randomised interventional trials of TPOAb positive euthyroid women [56,57], therefore commencing treatment with low doses of levothyroxine (25-50 μg daily) may be considered in TPOAb positive women with a history of recurrent pregnancy loss. For TPOAb negative women with SCH the relevant TSH thresholds providing weak or strong recommendation to initiate levothyroxine treatment are 4.0 mU/l and 10.0 mU/l respectively.

In cases of assisted reproductive techniques, such as intrauterine insemination (IUI) or in vitro fertilisation (IVF), SCH has been found to correlate with an adverse pregnancy outcome in a dose-dependent manner (higher the TSH levels, more the risks); furthermore levothyroxine treatment did result in a higher delivery rate [68]. Therefore, for women undergoing assisted reproductive techniques commencing treatment with low doses of levothyroxine (25-50 μg daily) is usually recommended in all SCH cases regardless of TPOAb, aiming to keep a TSH concentration <2.5 mU/L [6]. However, a TSH cut-off of 2.5UI/L or 4.5 UI/L in women who underwent IVF did not show differences in the rates of clinical pregnancy, delivery or miscarriage[6970].

Iodine deficiency is known to be deleterious for foetal development [30-32]. A recent study described negative effects in terms of foetal growth measured during gestation caused by both iodine deficiency and excess[71]. Therefore, the current guidelines recommend an assumption of iodine 250 μg daily in all pregnant women. However, this guidance does not apply to women on treatment with levothyroxine, since this drug already contains iodine[6].

According to the above reported observations, **Box 3** summarises the management of women diagnosed with gestational SCH and IH; however because of the difficulty to set precise cut-offs and definitions for gestational SCH and IH, there is no current

universal agreement about their clinical management[1]. **Figure 1** reports a clinical algorithm for gestational SCH based on TSH concentrations; current data about FT4 are still too weak to provide similar indications for IH. It has to be pointed out that recent findings also highlighted the risks of levothyroxine overtreatment, with FT4 levels even slightly above the reference range found to be associated with increased risk of reduced IQ [18] and AHDH [64]. Furthermore in mild hypothyroidism the thyroid function is not totally impaired as in OH, therefore physiological fluctuation may occur; for these reasons levothyroxine dose for SCH and IH treatment has to be low and body weight-adjusted where possible [1].

Box 3: Management of women diagnosed with gestational SCH or IH NOT on previous levothyroxine treatment

- Ensure a daily iodine intake of 250 μg using iodised salt or iodine supplements (only if NOT taking levothyroxine)
- SCH: see clinical algorithm Fig.1
- IH (normal TSH and FT4 <2.5-5th percentile): check TPOAb and consider commencing levothyroxine (25-50 μg daily) only if TPOAb positive and with a previous history of pregnancy loss.
- Monitor TSH and FT4 every 4 weeks

Conclusions

There is growing evidence that SCH, particularly in TPOAb positive women, merits treatment in pregnancy. There is considerable latitude with regard to treatment using the current ATA guidelines.

With regard to IH, it is well established it is a common phenomenon, it is more frequent in patients with obesity and those exposed to environmental toxins and it appears to negatively affect child motor and mental development. However, the underlying pathological mechanisms for its occurrence are less clear as are its effect on obstetric outcomes. The key issue to address is whether timely correction of IH with levothyroxine has substantial benefit with regard to neurological outcomes. Unfortunately, the trials undertaken to date have been relatively underpowered. As such only some clinicians favour treating IH during pregnancy and only in the first trimester.

Further trials are still needed to establish if *early* screening and treating for SCH and IH in pregnancy results in improved obstetric and offspring outcomes. It is also worth considering that many women established on levothyroxine prior to pregnancy do have elevated TSH levels during gestation[72]. As a result, these women have entirely preventable SCH; this is an important issue to address as higher gestational TSH levels were associated with increased odds of foetal loss[72].

388 Table 1: Summary of meta-analyses evaluating negative outcomes of subclinical
389 hypothyroidism (SCH) during pregnancy.
390

Study	Results
Zhang[73] (2017)	Foetal loss OR=1.90 (95%CI 1.59, 2.27)
Maraka[23] (2016)	Foetal loss OR =2.01 (95%CI 1.66, 2.44) Pre-term delivery OR=1.20 (95%CI 0.97, 1.50) Growth restriction OR=1.70 (95%CI 0.83, 3.50) Pre-eclampsia OR= 1.30 (95%CI 1.00, 1.68) Gestational diabetes OR=1.28 (95%CI 0.90, 1.81)
Gong[74] (2016)	Gestational diabetes OR=1.56 (95%CI 1.29, 1.88)
Toulis[75] (2014)	Gestational diabetes OR=1.39 (95%CI 1.07, 1.79)
Van den Boogaard[34] (2011)	Pre-eclampsia OR=1.70 (95%CI 1.10, 2.64) Gestational diabetes OR=1.40 (95%CI 0.64, 2.80)

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393 **Table 2: Summary of negative offspring outcomes associated with IH**
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Author (year)	**FT4 percentile used**	**Gestational week of testing**	**Study Endpoints**	**Key findings**
Pop (2003)	10th percentile	12, 24 32	Bayley mental and motor subscales at 12 and 24 months	IH at 12 weeks but not other time points were associated with lower Bayley mental and motor subscales.
Vermiglio (2004)	FT4 below the lower limit of local trimester-specific reference range	5, 10-14, 18-20	Neurological evaluation ADHD Full-scale IQ test	IH associated with increased risk of ADHD
Henrichs (2010)	10th percentile (mild) 5th percentile (severe)	13	Language delay, non-verbal cognitive delay	Both mild and severe IH were associated with language delay. Only severe language delay associated with non-verbal cognitive delay.
Craig (2012)	3rd percentile	15-20	Mental and motor development scales	No association with IH
Finken (2013)	10th percentile	12-13	response speed, response speed stability, visuomotor skills, response selection, response inhibition	IH associated with lower response speed
Julvez (2013)	5th percentile	8-20	Bayley mental and psychomotor scales	IH associated with lower mental but not psychomotor scores
Roman (2013)	10th percentile (mild) 5th percentile (severe)	13	Behavioural and emotional symptoms	Severe IH associated with high risk of likely autism

Korevaar (2013)	2.5th percentile	13	Premature delivery	IH associated with increased risk of premature delivery
Ghassabian (2014)	5th percentile	13	Nonverbal IQ test	IH associated with lower IQ
Modesto (2015)	5th percentile	13	ADHD	IH associated with increased risk of ADHD
Pakkila (2015)	FT4 below the lower limit of local trimester-specific reference range	10-11	School performances (self evaluation) ADHD Full-scale IQ test	IH associated with increased risk of suboptimal school performances
Gyllenberg (2016)	10th percentile	8-18	Schizophrenia	IH associated with increased risk of schizophrenia
Korevaar (2016)	Continuous measure	9-18	Non-verbal IQ test Brain morphology (MRI scans)	IH associated with lower IQ, grey matter and cortex volumes

ADHD = attention deficit hyperactivity disorder, FT4 = free-thyroxine, IQ = intelligence quotient, MRI = magnetic resonance imaging

399 **Table 3: Summary of key trials**
400

	CATS (2012)[60]	Casey (2017)[76]	Nazarpour (2018)[62]
Countries in trial	UK, Italy	USA	Iran
Number with low thyroid function	794	677	366
Placebo-controlled	No	Yes	No
Gestational age at recruitment (weeks)	Median (IQR) Screening 12.3 (11.6 -13.6) Controls 12.3 (11.6 – 13.5)	Mean (SD) Screening 16.6 (3.0) Controls 16.7 (3.0)	Mean (SD) Screening 11.4 (4.1) Controls 12.2 (4.3)
Baseline TSH (mU/l)	Median (IQR) Screening UK 3.8 (1.5-4.7) Screening Italy 3.1 (1.3-4.0) Controls UK 3.2 (1.2 – 4.2) Controls Italy 2,4 (1.3-3.9)	Mean (95%CI) Screening 4.5 (4.4-4.7) Control 4.3 (4.2 -4.5)	Median (IQR) Screening 3.8 (2.8 - 4.8) Control 3.6 (3.1- 4.1)
Outcomes assessed	IQ, behaviour obstetric outcomes*	Pregnancy outcomes, offspring IQ and behaviour	Preterm delivery
Benefit of initiating levothyroxine	No benefit with regard to IQ. Potential reduction in foetal loss. Caution with over-treatment.	No benefits observed with regard to pregnancy outcomes and offspring IQ	May reduce pre-term delivery at TSH levels > 4.0 mU/l

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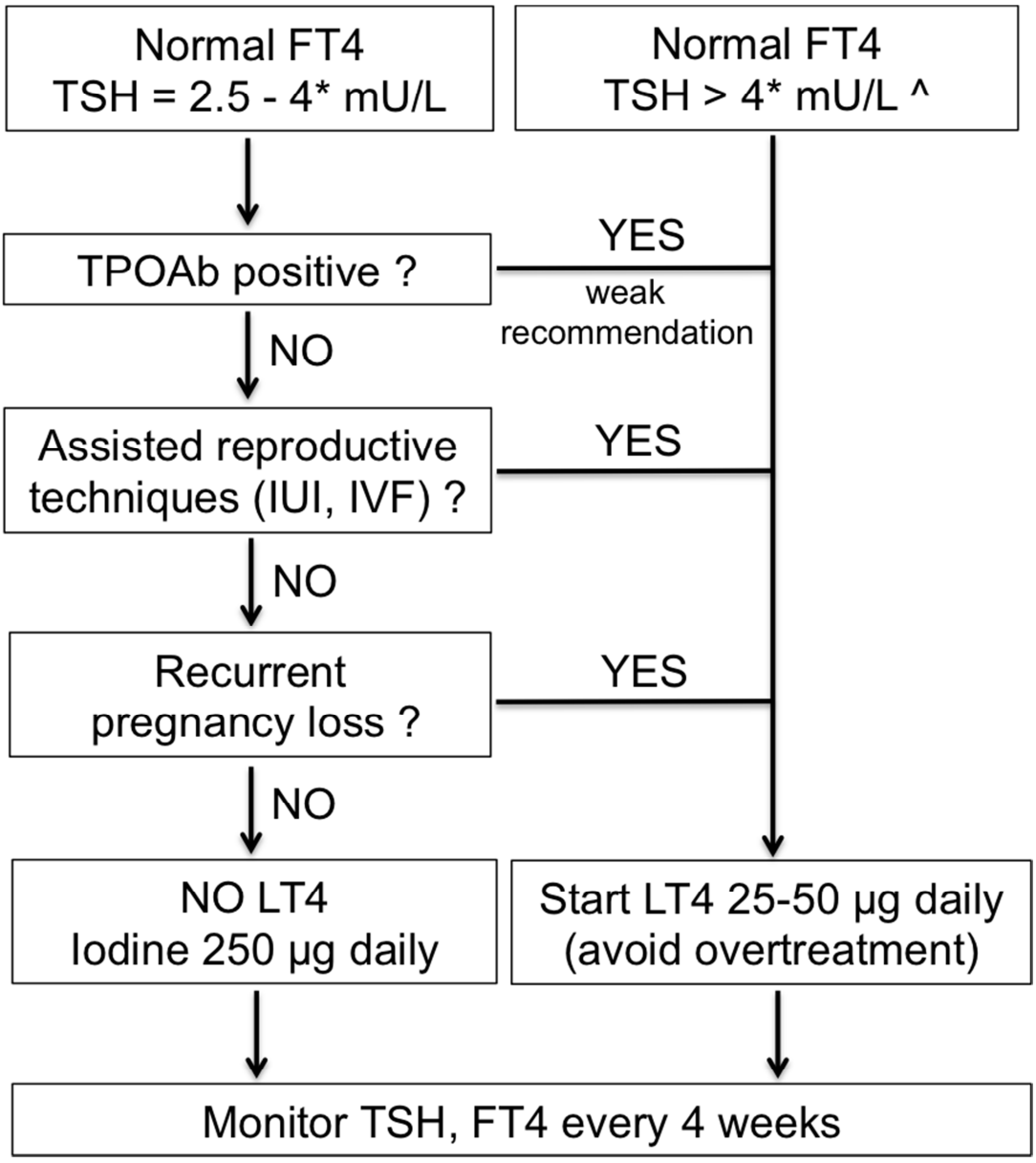
Figures

Figure 1: Algorithm for the clinical management of SCH



Legend: FT4 = Free-thyroxine, IUI = intrauterine insemination, IVF = in vitro fertilisation, LT4 = levothyroxine, TPOAb = autoantibodies to thyroid peroxidase, TSH = thyroid stimulating hormone

Notes:

* TSH = 4 mU/L or upper limit of pregnancy-specific reference range

^ In TPOAb positive women: always strong recommendation
In TPOAb negative women: TSH >4* mU/L: weak recommendation
TSH >10 mU/L: strong recommendation