Preconception management of thyroid dysfunction

Onyebuchi E Okosieme [1, 2], Ishrat Khan, and Peter N Taylor [1]

[1] Thyroid Research Group
Institute of Molecular and Experimental Medicine
School of Medicine, Cardiff University
Cardiff, CF14 4XN, UK

[2] Endocrine and Diabetes Department
Prince Charles Hospital
Cwm Taf University Health Board
Merthyr Tydfil, CF47 9DT, UK

Short title: Preconception and Thyroid

Keywords: Preconception, Hyperthyroidism, Hypothyroidism, Graves’ disease, Pregnancy, antithyroid drugs, Levothyroxine, Screening, Thyroid stimulating hormone (TSH), Thyroxine

Word count:

Number of tables:

Number of boxes:

Number of figures:

Address for correspondence
Dr Onyebuchi Okosieme MD FRCP
Endocrine and Diabetes Department
Prince Charles Hospital,
Cwm Taf University Health Board
Merthyr Tydfil, CF47 9DT
Email: OkosiemeOE@cardiff.ac.uk
Telephone: +441685728353
Fax: +441685728448
Abstract
Introduction
Thyroid disorders are common in women of reproductive age (1). Overt thyroid disease carries an increased risk of adverse pregnancy outcomes including miscarriages, stillbirths, and neuro-intellectual impairment in the offspring (2, 3). These adverse events also occur to some extent in patients with subclinical hypothyroidism (2). Crucially, the deleterious effects of overt disease are preventable by prompt correction of thyroid dysfunction (4-6). Thyroid hormones are essential for normal fetal growth and brain development and in early gestation the fetus wholly relies on maternal thyroxine delivery up until the onset of fetal thyroid hormone secretion at 14-18 weeks (7). This early phase of fetal life coincides with important developmental events such as neuronal migration, proliferation, and neural tube formation, and thus represents a period of critical vulnerability during which maternal thyroid dysfunction could have lasting repercussions (7). Effective preconception management is a key strategy for optimising thyroid disease outcomes in pregnancy but focused reviews on preconception care are scarce. In this review we highlight the rationale and evidence for current preconception strategies in the management of thyroid dysfunction.

Physiological adaptations of thyroid function in pregnancy
Normal pregnancy is characterised by a series of dynamic and highly orchestrated alterations in thyroid hormone economy (figure 1) (8). These changes are set in motion from the early post-conception period and adapt through gestation to increase fetal thyroid hormone delivery in the face of increased iodine requirements and peripheral hormone metabolism.
Increase in thyroid hormone production

Serum thyroxine binding globulin (TBG) concentrations start to rise from 6 weeks gestation primarily due to oestrogen induced increase in hepatic TBG synthesis (8). TBG is the major thyroid hormone transport protein in pregnancy and consequently T4 and T3 concentrations increase in parallel, reaching peak levels by mid gestation. Levels of free thyroid hormones may fall to a small degree but are generally maintained within the normal range in healthy women with adequate iodine nutrition and thyroid function (9). Increased thyroid hormone production also results from the thyroid stimulatory actions of placental derived human chorionic gonadotropin (hCG). hCG has an identical α-subunit to TSH, and so acts on TSH receptors on thyroid follicular cells to increase thyroidal T3 and T4 output. The increase in thyroid hormone production is in turn accompanied by a fall in serum TSH via pituitary thyroid feedback and trough TSH concentrations are reached by 10-12 weeks. Lastly, increased thyroid hormone requirements are amplified by thyroid hormone peripheral metabolism by the type III inner-ring deiodinase, abundantly expressed in placental tissue (8).

Increase in Iodine requirements

Iodine requirements increase in pregnancy primarily due to increased renal clearance with additional feto-placental losses in later gestation. The thyroid gland compensates for these losses by increasing thyroidal iodide uptake and clearance. Pregnant women with sufficient iodine nutrition are able to seamlessly implement these adaptive mechanisms but in iodine deficient states these changes may fail to deliver adequate thyroid hormones to the fetus. Population iodine nutrition remains highly variable and even in countries with iodine sufficient status some pregnant women do not achieve the minimum recommended daily iodine intake of 250 mcg
European and American endocrine society guidelines recommend antenatal supplementation of 150 mcg of iodine daily but specific recommendations in the UK are lacking (10-12).

**Laboratory implications**

The above physiological changes result in a downward shift of gestational TSH reference intervals. This change is most marked in the first trimester and varies with race and ethnicity. Current guidelines recommend the use of trimester specific normative values derived from a representative healthy pregnant population but such data is not widely available. A pragmatic TSH upper limit of 2.5 mU/L was previously advocated but recent data now shows this to be too low (13). One approach suggested in the current guidelines of the American Thyroid Association (ATA) is to set the pregnancy reference range at 0.5 mU/L and 0.4 mU/L below the upper and lower non-pregnant reference range respectively, reflecting the anticipated magnitude of the TSH drop (11). With respect to FT4, the commonly used immunoassays are prone to method dependent bias in pregnancy due to changes in TBG and albumin concentrations (11, 14). Total T4 is a more predictable alternative as it typically rises by 50% of baseline values attaining peak levels by 16 weeks gestation (11). More robust methods such as equilibrium dialysis, liquid chromatography-tandem mass spectrometry (LC-MS/MS), or FT4 index calculations are cumbersome to perform and not routinely used (11).

**Overt hypothyroidism**

Overt hypothyroidism (i.e. low FT4 and elevated TSH) affects 0.3 – 0.5% of the population and is ten times more prevalent in females than in males (15). In iodine-replete countries hypothyroidism is predominantly due to Hashimoto’s thyroiditis characterised by the presence of circulating thyroid-specific antibodies namely
thyroid peroxidase (TPOAb) and thyroglobulin (TgAb) antibodies. Other common causes include thyroidectomy and radioiodine therapy for benign and malignant thyroid disease, and globally, iodine deficiency remains relevant in areas with severe deficiency. Uncorrected overt hypothyroidism increases the risk of adverse pregnancy outcomes such as miscarriages, eclampsia, anaemia, and pre-term births (16, 17). The effect of maternal hypothyroidism also affects neuro-intellectual and behavioural development in the child (2, 16, 17).

There is consensus that overt gestational hypothyroidism should be corrected although prospective controlled trials are lacking and would be unethical in the light of current understanding. However, we can surmise from available observational data that it is beneficial to correct gestational hypothyroidism. Several small prospective open labelled studies have shown that correction of overt hypothyroidism to TSH levels within the reference range yields significant gains in reducing fetal loss (4, 18). An analysis of a large community database of levothyroxine-treated women showed an incremental increase in miscarriage risk in association with rising TSH strata, with the highest risk seen at early gestation TSH concentrations exceeding 10 mU/L (OR 3.95, 95% CI 1.87, 8.37) (6).

Preconception management of hypothyroidism

The goal of preconception management is to correct hypothyroidism, provide pre-pregnancy counselling, and pre-emptively increase levothyroxine dose on conception. In the absence of a functioning thyroid gland most women with hypothyroidism will require an increase in levothyroxine dose to meet gestational demands. Studies report a 30-50% increase in requirements although the magnitude of this increase and the proportion of patients requiring dose increases is more variable (19-21). In practice 25-50% of women have TSH values outside the
references ranges in early pregnancy (6, 22, 23) in part due to the post-conception TSH rise (23-25) but also a reflection of inadequate thyroid hormone replacement in the general population (26, 27). Women with a new diagnosis of hypothyroidism should be commenced on full replacement doses of levothyroxine (0.8-1.6 mcg/kg/day) and advice should be provided on the importance of treatment adherence and the need to optimise thyroid hormone replacement before conception. Patients should be reassured that levothyroxine is safe in pregnancy and that satisfactory pregnancy outcomes are achieved with adequate replacement. Liothyronine or desiccated thyroid preparations are not recommended in pregnancy as T3 is wholly degraded in the placenta.
The preconception TSH target should be similar to the first trimester target of <2.5 mU/L for levothyroxine treated women (11). Other limits may be more appropriate where gestation-specific reference ranges are available (11). Women on levothyroxine should be instructed to obtain a thyroid function test and to increase their levothyroxine dose once pregnancy is confirmed. Several empirical approaches to this has been suggested including doubling the levothyroxine dose for two days a week, equating to a 30% increase (20) or increasing the dose by 25 mcg daily in patients receiving 100 mcg daily or less and by 50 mcg in those receiving more than 100 mcg (2). In our practice we favour the latter approach which approximates to increases of 25-50%. Two small studies have demonstrated that aiming for a low-normal preconception TSH (<1.2 mU/L) guarantees a post conception TSH<2.5 mU/L (24, 25) but the safety of this approach in non-specialist settings requires confirmation. Additional dose adjustments may be required depending on the conception thyroid test and it is important that local arrangements are in place to enable ready access to healthcare services on conception.

Subclinical hypothyroidism

Unlike overt hypothyroidism it is less certain whether patients with subclinical hypothyroidism should be treated with levothyroxine. Subclinical hypothyroidism affects 2-3% of pregnant women although higher rates are reported when stringent upper TSH limits are applied (28). Progression rates from subclinical to overt disease is 2-5% per year and is amplified in individuals with positive TPOAb or TSH concentration >10 mU/L (15). In pregnancy a quarter of women with subclinical hypothyroidism have persistent TSH elevation five years after delivery (29). The fetomaternal risks associated with overt hypothyroidism are also seen with subclinical hypothyroidism (4) and have been addressed in numerous largely retrospective
studies marked by disparities in diagnostic TSH thresholds, study endpoints, and timing of assessments (1, 30, 31). Meta-analysis of these studies suggest a significant risk of miscarriage and pre-term loss in women with gestational subclinical hypothyroidism (2). Recent data from a Chinese national health programme (n=184,611 women) showed that even a TSH >2.5 mU/L in the six months before conception was associated with small but significant risks of miscarriages and pre-term delivery (31).

However, despite the wealth of observational data only a few interventional trials have been published (table 1). A controlled trial by Negro et al showed that screening and correction of gestational subclinical hypothyroidism (TSH>2.5 mU/L) in women classified as low risk for thyroid disease significantly reduced adverse pregnancy events compared to no treatment at all (OR ratio 0.43, 95% CI, 0.26, 0.70).(32). Another study with a cluster trial design showed significant reduction in miscarriage and fetal macrosomia rates from treating subclinical hypothyroidism (TSH 2.5-10.0 mU/L) (33). In contrast one observational study reported no difference in rates of pregnancy loss between women with subclinical hypothyroidism who received levothyroxine and those who did not (34). A 2017 retrospective cohort study using an administrative US database comprising 5405 women with subclinical hypothyroidism (TSH 2.5-10.0 mU/L) observed that treatment of subclinical hypothyroidism led to reductions in pregnancy loss but surprisingly showed an increased risk of pre-term delivery, gestational diabetes, and eclampsia (35).

Two well-conducted randomised controlled trials investigated the benefits of maternal screening and levothyroxine treatment on child cognition (36). The controlled antenatal thyroid screening study (CATS) randomised 21,846 pregnant
women to a screening or control group and treated the screened group with levothyroxine if they had subclinical hypothyroidism or hypothyroxinaemia (36). IQ scores evaluated at 3 years were not different between offspring of treated and untreated women. In the second study 677 women with subclinical hypothyroidism and 526 with hypothyroxinaemia were randomly assigned to receive levothyroxine or placebo (37). Similarly, no differences in IQ were observed between children of treated and untreated mothers tested from 3-5 years of age. Pooled analysis of both trials (38) as well as a follow-up evaluation of the CATS child cohort at nine years also failed to show differences in IQ scores (39). Several explanations have been proposed to reconcile these findings including late treatment initiation (median gestational age 13-18 weeks), possible over-treatment (CATS cohort), and high loss to follow up (CATS cohort).

Thus, pending further trials there is insufficient evidence to support a consistent therapeutic policy for gestational subclinical hypothyroidism. In agreement with most international guidelines we recommend treating women with positive antibodies, TSH >10 mU/L, and other risk factors for thyroid dysfunction (table 3). Women with infertility or recurrent pregnancy loss should be offered levothyroxine on the basis that it could potentially improve fertility and delivery rates (40, 41). Treatment should also be considered in women who do not fall into any of the risk categories. It is reasonable to discuss the uncertainties with the patient and reach a shared decision taking into account the potential but unproven benefits of therapy together with the safety of levothyroxine in pregnancy when carefully monitored in a specialist antenatal clinic. It should be noted that the definition of subclinical hypothyroidism in the preconception stage should be based on the non-pregnant reference range and
not the ATA treatment threshold of 2.5 mU/L. More so, borderline results should be re-checked 6-8 weeks later before establishing the diagnosis.

**Isolated hypothyroxinaemia**

Isolated hypothyroxinaemia refers to the biochemical finding of a low FT4 in conjunction with a normal TSH concentration (42). The aetiology of this condition is unclear but contributory factors in pregnancy include iodine deficiency, thyroid autoimmunity, assay techniques, and maternal characteristics such as age, body mass index, and co-existent diabetes (42, 43). The prevalence ranges from 1-10% in iodine sufficient countries to 20-30% in deficient areas and depends on the diagnostic FT4 threshold as well as the iodine nutrition status of the population (44).

There is evidence that maternal hypothyroxinaemia adversely affects child cognitive and behavioral development. Pop and colleagues reported an 8–10 point deficit in mental and motor function scores in infants of women with persistent hypothyroxinaemia at 12 weeks gestation compared to children of euthyroid mothers (16). Subsequent studies have shown adverse links between hypothyroxinaemia and offspring IQ (45), educational performance (46), attention deficit hyperactivity disorders (47), and child behavioural problems (48). In a population based prospective study involving 3839 mother child pairs Korevaar *et al* elegantly demonstrated an inverted U shaped association between maternal T4 and child IQ with deficits of 1.4 – 3.8 points at extremes of FT4 concentrations (45). The association with obstetric outcomes is less consistent with some studies reporting adverse pregnancy outcomes (49) while others have shown no association with adverse perinatal effects (50).
Presently there is no evidence that correcting hypothyroxinaemia with levothyroxine has any benefits on child neuro-intellectual function. The two randomized controlled trials to have addressed this subject to date showed no benefits of maternal levothyroxine on child IQ in women with gestational hypothyroxinaemia (36, 37, 39). Thus preconception treatment is not recommended (11) although some guidelines would consider treatment in early pregnancy (12). As with other uncertainties shared treatment decisions can be reached following an open discussion regarding the lack of evidence in this area.

**Euthyroid thyroid autoimmunity**

About 10% of pregnant women have positive thyroid antibodies without thyroid dysfunction although prevalence rates vary according to ethnicity and iodine nutrition (1). Thyroid autoimmunity is more common in women with infertility and recurrent pregnancy loss (51), and about a fifth of untreated antibody positive women develop an elevated TSH during the course of pregnancy (5) indicating a degree of thyroid hormone deficiency. Observational studies have shown an increased risk of miscarriages, pre-term birth, and child neuro-intellectual deficits in pregnant women with thyroid antibodies (TPOAb) (52) although this association was not confirmed in some studies (53). However, the results of meta-analyses support an overall increased risk of pregnancy loss in association with maternal thyroid autoimmunity (54-56). A cause-effect relationship is unproven but suggested mechanisms include the possibility of innate thyroid hormone deficiency, induction of a diffuse autoimmune process that promotes rejection of the fetal allograft, and the confounding effects of older age in antibody-positive women (57).

Whether levothyroxine can prevent foetal loss in antibody positive women is unproven. Negro et al showed that miscarriage rates in untreated euthyroid TPOAb-
positive pregnant women was higher than in antibody-positive women who received levothyroxine (13.8% vs.3.5%) (5). In a similarly designed study, Nazarpour et al saw a reduction in pre-term delivery rates in treated antibody-positive women (58). Other trials did not confirm these benefits (59, 60) and levothyroxine had no impact on pregnancy loss in TPOAb positive women with TSH<2.5 mU/L (61). Thus, there is currently no strong evidence to support routine levothyroxine therapy for women with thyroid autoimmunity. Nonetheless, thyroid function should be monitored through pregnancy due to the risk of thyroid dysfunction. Two randomised controlled trials, the UK TABLET study, and the T4Life trial in Holland, are currently investigating the effects of Levothyroxine on live birth rates in women with recurrent pregnancy loss.

**Hyperthyroidism**

Hyperthyroidism is diagnosed in 0.1 – 1.0% of all pregnancies in iodine sufficient countries (62). The vast majority of cases are due to Graves’ disease although other causes like solitary and multiple autonomously functioning nodules are occasionally seen in pregnancy (62). In Graves’ disease, hyperthyroidism results from unregulated stimulation of the TSH receptor by TRAbs, the pathological disease hallmark (63). Three well-established therapies for hyperthyroidism namely antithyroid drugs, radioactive iodine, and thyroidectomy have been available for over half a century (64). However, therapeutic options in pregnancy are limited to antithyroid drugs since radioactive iodine therapy is contraindicated in pregnancy and thyroidectomy is rarely used due the risk of surgical morbidity and fetal exposure to anaesthetic gases. In pregnancy the combination of maternal hyperthyroidism, circulating maternal TRAbs, and antithyroid drug therapy, present significant threats to fetal and maternal well-being (figure 3).

*Maternal hyperthyroidism*
Uncontrolled hyperthyroidism exerts well recognised effects that includes miscarriages, stillbirths, intrauterine growth retardation, maternal hypertension, and heart failure (65, 66). These associations were originally documented in early hospital series (67) and have subsequently been confirmed in large population datasets (68). Women with severe uncontrolled hyperthyroidism may also develop cardiovascular complications including hypertension, arrhythmias, and cardiac failure (69). Adverse effects are typically seen in association with overt hyperthyroidism (elevated FT4 and suppressed TSH) but not with subclinical hyperthyroidism (normal FT4 and suppressed TSH) (70) which in most instances reflects the normal physiological adaptations in pregnancy.

**Maternal TRAbs**

In pregnancy circulating maternal TRAbs cross the placenta and can induce fetal thyroid dysfunction through actions on TSH receptors on the fetal thyroid gland (71, 72). Maternal TRAbs are predominantly stimulatory and cause fetal hyperthyroidism and goiter although hypothyroidism occasionally occurs from the presence of TRABs with inhibitory properties (72). The prevalence of fetal hyperthyroidism is difficult to ascertain but hyperthyroidism occurs in about 1-5% of neonates of mothers with Graves’ disease (73). Although neonatal hyperthyroidism is typically transient it can result in significant morbidity with occasional fatality if unrecognised (73). An important consideration is that pregnant women with previous Graves’ disease who were rendered hypothyroid by radioactive iodine therapy or surgery may continue to harbour TRAbs thus placing the fetus at risk of thyroid dysfunction (74). In a five year prospective study, persistence of TRAb levels 18 months after therapy was seen in 75% of radioactive iodine treated patients compared to 30% of post-surgical patients and 3% of women rendered euthyroid with antithyroid drugs (74).
Antithyroid drugs

The thionamide compounds namely methimazole (MMI), its pro-drug derivative, carbimazole (CMZ), and propylthiouracil (PTU) represent the mainstay of therapy for hyperthyroidism in pregnancy (75). These compounds reduce thyroid hormone secretion through inhibition of thyroid peroxidase coupling and iodination of tyrosine residues on thyroglobulin (75). They also have immunosuppressive properties and in large doses PTU blocks peripheral T4 to T3 conversion (75). CMZ is available in the UK while MMI is prescribed in the US and continental Europe. Outside of pregnancy MMI or CMZ (CMZ/MMI) is first line therapy due to a more favourable pharmacokinetic and safety profile. Both drugs cross the placenta to the same extent and are secreted in breast milk with negligible effects on the thyroid function of breast fed neonates (75).

About 1-5% of patients treated with antithyroid drugs report minor reactions such as rash and fever, which resolve with discontinuation and switching to an alternative drug (76). Agranulocytosis is a potentially more serious problem that occurs in 0.1-0.2% of antithyroid drug users particularly patients on high-dose regimens. It develops abruptly and is difficult to predict even with routine blood count monitoring. Affected patients should stop thionamides and treatment with broad spectrum antibiotics is usually required (76). PTU is associated with a potentially fatal liver toxicity that occurs in about 1 per 1000 treated pregnant women per year (77). In one US series, 22 episodes of PTU related liver failure comprising nine deaths and five liver transplants were observed over a 20 year period (78). The course of PTU related hepatotoxicity can be catastrophic in pregnancy and a review of six reported cases revealed one fatality and two liver transplants (76). Early recognition of cases
offers the best hope of survival although the risk of hepatotoxicity is difficult to predict from clinical and biochemical monitoring.

Another concern regarding thionamide use in pregnancy is the risk of congenital anomalies. CMZ/MMI is associated with CMZ or MMI embryopathy, a classic cluster of anomalies comprising aplasia cutis, choanal atresia, trachea-oesophageal fistula, and dysmorphic facial features (79). This association was originally reported in small case series but the use of large disease registries have now revealed a more varied phenotype (80). Analysis of a Danish birth registry showed a prevalence of birth defects following intrauterine exposure to PTU and CMZ/MMI which was 2-4% higher than in unexposed children (81). Furthermore, a less severe pattern of anomalies was observed for PTU exposure comprising renal tract and head and neck anomalies (81). The increased risk of birth defects in association with PTU as well as CMZ/MMI exposure has since been confirmed in two meta-analysis published in 2015 (82, 83) as well as in a recently published study from a large Korean health database (84).

The above considerations have therefore shaped current policy on the management of gestational hyperthyroidism with the goal being to control hyperthyroidism and at the same time limit feto-maternal drug exposure (11). Antithyroid drugs should be used at the least effective dose that maintains normal thyroid status and where treatment is indicated PTU is recommended in the first trimester of pregnancy thereby reducing the risk of CMZ/MMI associated teratogenicity. Patients can then switch to CMZ/MMI after the first trimester thus curtailting the risk of PTU related hepatotoxicity for the remainder of pregnancy. Further studies are needed to clarify the safety and effectiveness of this approach since some studies have shown that
switching thionamides during pregnancy does not modify anomaly risk (81-83). A review by Laurberg and Andersen identified a high-risk window from gestation week 6-10 during which antithyroid drug exposure carried the greatest risk of birth defects (85) underpinning the need for an effective preconception strategy.

**Preconception management of hyperthyroidism**

The aim of preconception management is to minimise the risk of maternal hyperthyroidism and antithyroid drug exposure in subsequent pregnancy (11, 14, 86). Women of child bearing age with active hyperthyroidism should be counseled on the risk of fetal harm from uncontrolled hyperthyroidism and advised to delay pregnancy with effective contraception until a stable euthyroid state is achieved (11, 14). Specific instructions should be provided for all women to inform their healthcare practitioners immediately pregnancy is confirmed (11). Definitive therapy with radioiodine or surgery is an option for women who intend future pregnancy (11, 14) since pregnancy may induce relapse following antithyroid therapy (87). Definitive therapy is most suited to women with a high risk of relapse i.e. positive TRAb levels, goiter, ophthalmopathy, and severe biochemical disease (figure 4) (64, 88). It is important that pregnancy is avoided for six months after radioiodine treatment due to the potential for fetal harm from radioiodine exposure (11, 14). Total thyroidectomy may be preferable in individuals with high risk of relapse since thyroidectomy is usually although not invariably followed by disappearance of circulatory TRAbs (74).

Several approaches can be adopted in women who are actively trying to conceive while still undergoing treatment with antithyroid drugs (89). One option is to switch such women from CMZ/MMI to PTU since PTU is the preferred treatment in the first trimester (14). Alternatively, MMI/CMZ may be continued up till conception and then
switched as early as possible on conception to PTU. This approach restricts the use of PTU to the first trimester of pregnancy thus reducing the risk of PTU related hepatotoxicity (14). The third approach is to stop antithyroid drugs on conception in women with a low risk of relapse i.e. negative TRAb levels, no goiter no ophthalmopathy, and low dose thionamide requirements (14) (figure 4). Such women should then be monitored for relapse with 2-4 weekly thyroid tests in the immediate post-conception period. Patients on the combination of CMZ/MMI and levothyroxine should be switched to a titration regimen since the high doses of antithyroid drugs could potentially cause fetal hypothyroidism in pregnancy.

**Patients with infertility**

Thyroid dysfunction is associated with varying degrees of gonadal dysfunction which are reversible with treatment but are less commonly observed nowadays due to earlier disease detection and treatment. (1). Thyrotoxicosis increases sex hormone binding globulin (SHBG) concentrations as well as total testosterone, oestradiol, and basal and GnRH stimulated gonadotrophin levels while reverse changes are observed in hypothyroidism (1). Males with thyroid dysfunction have shown reduced libido, erectile dysfunction and defects in spermatogenesis, while reduced conception rates, anovulatory cycles, and disruption in embryo implantation have been described in women (1).

The reported prevalence of subclinical hypothyroidism in fertility clinic studies varies widely (0.7% to 43%) reflecting discrepancies in assay sensitivities and diagnostic criteria (90). In one study women who had unsuccessful fertilisation had a higher mean TSH level compared to those who achieved fertilisation (91). The prevalence of thyroid autoimmunity was also increased in women attending fertility clinics compared to controls (14 vs 8%) (92). A systematic review of 12 studies showed
detrimental effects of thyroid autoimmunity on live birth rates (55). Furthermore, a small number of trials in fertility clinic patients with subclinical hypothyroidism (40, 41) or thyroid autoimmunity (60) showed that levothyroxine therapy improved pregnancy delivery rates (56). Lastly, hypothyroidism can be induced by controlled ovarian stimulation used in preparation for artificial reproduction technology (ART) procedures. The mechanism of hypothyroidism following ovarian stimulation is believed to be due to the oestrogen surge which increases TBG concentrations thereby exaggerating the fall in free thyroid hormone levels and the compensatory rise in TSH (90).

Patients with infertility should therefore be screened for thyroid dysfunction including TPOAb measurements. Infertility clinic patients with overt disease should be treated aiming for the first trimester TSH of <2.5 mU/L. Women with subclinical hypothyroidism should also be offered treatment taking into account the potential for benefit and the possibility that pregnancy could worsen thyroid dysfunction. Similar considerations apply to women with thyroid autoimmunity and a small dose of 25-50 mcg is appropriate in this group of patients (11).

**Universal preconception screening**

Current international guidelines do not recommend routine thyroid screening in pregnancy or the preconception period, except in women at risk of thyroid dysfunction, the so called case finding strategy (11). The rationale behind this approach is that the bulk of thyroid disorders in pregnancy are asymptomatic subclinical disease with no proven benefits of therapy and that screening could generate anxiety and present a risk of harm from over-treatment (93). The argument in favour of universal screening however is that thyroid dysfunction is common in pregnancy, adversely affects feto-maternal outcomes, and is easily treated with
established cost-effective therapies (93). Furthermore, a third of women with gestational thyroid dysfunction are not identified with existing case-finding strategies (94) which is less cost-effective than universal screening (95). In reality current clinical practice is approaching universal screening driven by increasing public and clinician awareness (96). In one hospital study, 85% of pregnant women had thyroid tests performed (96) and almost half of European thyroidologists reported that they screened all women in pregnancy (97). Further studies are required to understand current screening practices as non-systematic screening could ultimately result in care inequities with the risk of neglecting disadvantaged populations.

**Conclusions**

Endocrinologists and general clinicians will increasingly encounter women with thyroid disorders many of whom will require preconception advice. Optimal administrative set-ups for preconception services will vary with local resources but because many pregnancies are unplanned clinicians should address future pregnancy during routine clinical encounters. Further studies are required to determine best policy in women with subclinical hypothyroidism, hypothyroxinaemia, and thyroid autoimmunity as well as safe strategies for antithyroid drug use in the peri-conception period. The controversies regarding thyroid disease screening are unlikely to be resolved without additional adequately powered trials. A preconception recruitment design will be central to the success of future studies and although this will be challenging to achieve, recruitment hurdles could be overcome through collaborative multinational efforts.
FIGURES AND TABLES

Figure 1: Adaptations in thyroid physiology in pregnancy
Figure 2: Fetal Maternal interactions in hyperthyroidism in pregnancy
Figure 3: Preconception management of hyperthyroidism
Table 1: Preconception management of hypothyroidism Pete
Table 2: Randomised controlled trials of levothyroxine therapy in subclinical hypothyroidism in pregnancy Pete
Table 3: Patient Groups at risk of thyroid dysfunction Ishrat
REFERENCES


