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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

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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 fetoplacental 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

daily (10). 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 T4Lifetrial 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 radioiodine 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 radioiodine 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 fetomaternal 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 curtailing 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 fetomaternal 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.

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REFERENCES

1. Krassas GE, Poppe K, Glinoe D. Thyroid Function and Human Reproductive Health. *Endocrine Reviews*. 2010;31(5):702-55.
2. Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. *Clin Endocrinol (Oxf)*. 2015;82(3):313-26.
3. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstetrics and gynecology*. 2005;105(2):239-45.
4. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid*. 2002;12(1):63-8.
5. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab*. 2006;91(7):2587-91.
6. Taylor PN, Minassian C, Rehman A, Iqbal A, Draman MS, Hamilton W, et al. TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. *J Clin Endocrinol Metab*. 2014;99(10):3895-902.
7. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of maternal thyroid hormones during gestation on fetal brain development. *Neuroscience*. 2017;342:68-100.
8. Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev*. 1997;18(3):404-33.
9. Brent GA. Maternal thyroid function: interpretation of thyroid function tests in pregnancy. *Clin Obstet Gynecol*. 1997;40(1):3-15.
10. Taylor PN, Vaidya B. Iodine supplementation in pregnancy - is it time? *Clin Endocrinol (Oxf)*. 2016;85(1):10-4.
11. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid*. 2017;27(3):315-89.
12. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3(2):76-94.
13. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? *Clin Chem*. 2015;61(5):704-13.

14. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016;26(10):1343-421.
15. Vanderpump MP. The epidemiology of thyroid disease. *British medical bulletin*. 2011;99:39-51.
16. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol (Oxf)*. 2003;59(3):282-8.
17. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *The New England journal of medicine*. 1999;341(8):549-55.
18. Hallengren B, Lantz M, Andreasson B, Grennert L. Pregnant women on thyroxine substitution are often dysregulated in early pregnancy. *Thyroid*. 2009;19(4):391-4.
19. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *The New England journal of medicine*. 2004;351(3):241-9.
20. Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. *J Clin Endocrinol Metab*. 2010;95(7):3234-41.
21. Kothari A, Girling J. Hypothyroidism in pregnancy: pre-pregnancy thyroid status influences gestational thyroxine requirements. *Bjog*. 2008;115(13):1704-8.
22. Vadiveloo T, Mires GJ, Donnan PT, Leese GP. Thyroid testing in pregnant women with thyroid dysfunction in Tayside, Scotland: the thyroid epidemiology, audit and research study (TEARS). *Clin Endocrinol (Oxf)*. 2013;78(3):466-71.
23. Khan I, Wiczak JK, Hadjieconomou S, Okosieme OE. Preconception thyroid-stimulating hormone and pregnancy outcomes in women with hypothyroidism. *Endocr Pract*. 2013;19(4):656-62.
24. Rotondi M, Mazziotti G, Sorvillo F, Piscopo M, Cioffi M, Amato G, et al. Effects of increased thyroxine dosage pre-conception on thyroid function during early pregnancy. *Eur J Endocrinol*. 2004;151(6):695-700.
25. Abalovich M, Alcaraz G, Kleiman-Rubinsztein J, Pavlove MM, Cornelio C, Levalle O, et al. The relationship of preconception thyrotropin levels to requirements for increasing the levothyroxine dose during pregnancy in women with primary hypothyroidism. *Thyroid*. 2010;20(10):1175-8.
26. Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing

benefits and risks: evidence from a large community-based study. *JAMA Intern Med.* 2014;174(1):32-9.

27. Okosieme OE, Belludi G, Spittle K, Kadiyala R, Richards J. Adequacy of thyroid hormone replacement in a general population. *QJM.* 2011;104(5):395-401.

28. Moreno-Reyes R, Glinoeer D, Van Oyen H, Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. *J Clin Endocrinol Metab.* 2013;98(9):3694-701.

29. Shields BM, Knight BA, Hill AV, Hattersley AT, Vaidya B. Five-year follow-up for women with subclinical hypothyroidism in pregnancy. *J Clin Endocrinol Metab.* 2013;98(12):E1941-5.

30. Okosieme OE, Marx H, Lazarus JH. Medical management of thyroid dysfunction in pregnancy and the postpartum. *Expert Opin Pharmacother.* 2008;9(13):2281-93.

31. Chen S, Zhou X, Zhu H, Yang H, Gong F, Wang L, et al. Preconception TSH and pregnancy outcomes: a population-based cohort study in 184 611 women. *Clin Endocrinol (Oxf).* 2017;86(6):816-24.

32. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab.* 2010;95(4):1699-707.

33. Ma L, Qi H, Chai X, Jiang F, Mao S, Liu J, et al. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. *J Matern Fetal Neonatal Med.* 2016;29(9):1391-4.

34. Wang S, Teng WP, Li JX, Wang WW, Shan ZY. Effects of maternal subclinical hypothyroidism on obstetrical outcomes during early pregnancy. *J Endocrinol Invest.* 2012;35(3):322-5.

35. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. *Bmj.* 2017;356:i6865.

36. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. *The New England journal of medicine.* 2012;366(6):493-501.

37. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. *The New England journal of medicine.* 2017;376(9):815-25.

38. Thompson W, Russell G, Baragwanath G, Matthews J, Vaidya B, Thompson-Coon J. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2018.

39. Hales C, Taylor PN, Channon S, Paradise R, McEwan K, Zhang L, et al. Controlled Antenatal Thyroid Screening II: effect of treating maternal sub-optimal thyroid function on child cognition. *J Clin Endocrinol Metab*. 2018.
40. Kim CH, Ahn JW, Kang SP, Kim SH, Chae HD, Kang BM. Effect of levothyroxine treatment on in vitro fertilization and pregnancy outcome in infertile women with subclinical hypothyroidism undergoing in vitro fertilization/intracytoplasmic sperm injection. *Fertility and sterility*. 2011;95(5):1650-4.
41. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. *Endocr Pract*. 2010;16(5):792-7.
42. Negro R, Soldin OP, Obregon MJ, Stagnaro-Green A. Hypothyroxinemia and pregnancy. *Endocr Pract*. 2011;17(3):422-9.
43. Furnica RM, Gruson D, Lazarus JH, Maiter D, Bernard P, Daumerie C. First trimester isolated maternal hypothyroxinaemia: adverse maternal metabolic profile and impact on the obstetrical outcome. *Clin Endocrinol (Oxf)*. 2017;86(4):576-83.
44. Moleti M, Trimarchi F, Vermiglio F. Doubts and Concerns about Isolated Maternal Hypothyroxinemia. *Journal of thyroid research*. 2011;2011:463029.
45. Korevaar TI, Muetzel R, Medici M, Chaker L, Jaddoe VW, de Rijke YB, et al. Association of maternal thyroid function during early pregnancy with offspring IQ and brain morphology in childhood: a population-based prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4(1):35-43.
46. Noten AM, Loomans EM, Vrijkotte TG, van de Ven PM, van Trotsenburg AS, Rotteveel J, et al. Maternal hypothyroxinaemia in early pregnancy and school performance in 5-year-old offspring. *Eur J Endocrinol*. 2015;173(5):563-71.
47. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *J Clin Endocrinol Metab*. 2004;89(12):6054-60.
48. Ghassabian A, Bongers-Schokking JJ, Henrichs J, Jaddoe VW, Visser TJ, Visser W, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. *Pediatric research*. 2011;69(5 Pt 1):454-9.
49. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstetrics and gynecology*. 2008;112(1):85-92.
50. Casey BM, Dashe JS, Spong CY, McIntire DD, Leveno KJ, Cunningham GF. Perinatal significance of isolated maternal hypothyroxinemia identified in the first half of pregnancy. *Obstetrics and gynecology*. 2007;109(5):1129-35.
51. Poppe K, Velkeniers B, Glinde D. The role of thyroid autoimmunity in fertility and pregnancy. *Nat Clin Pract Endocrinol Metab*. 2008;4(7):394-405.

52. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity in the first trimester of pregnancy is associated with negative pregnancy outcomes. *J Clin Endocrinol Metab.* 2011;96(6):E920-4.
53. Unuane D, Velkeniers B, Bravenboer B, Drakopoulos P, Tournaye H, Parra J, et al. Impact of thyroid autoimmunity in euthyroid women on live birth rate after IUI. *Hum Reprod.* 2017;32(4):915-22.
54. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ.* 2011;342:d2616.
55. Busnelli A, Paffoni A, Fedele L, Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: a systematic review and meta-analysis. *Human reproduction update.* 2016;22(6):775-90.
56. Velkeniers B, Van Meerhaeghe A, Poppe K, Unuane D, Tournaye H, Haentjens P. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. *Human reproduction update.* 2013;19(3):251-8.
57. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol.* 2004;150(6):751-5.
58. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol.* 2017;176(2):253-65.
59. Wang H, Gao H, Chi H, Zeng L, Xiao W, Wang Y, et al. Effect of Levothyroxine on Miscarriage Among Women With Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo Transfer: A Randomized Clinical Trial. *Jama.* 2017;318(22):2190-8.
60. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Hum Reprod.* 2005;20(6):1529-33.
61. Negro R, Schwartz A, Stagnaro-Green A. Impact of Levothyroxine in Miscarriage and Preterm Delivery Rates in First Trimester Thyroid Antibody-Positive Women with TSH<2.5mIU/L. *J Clin Endocrinol Metab.* 2016;jc20161803.
62. Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. *Eur J Endocrinol.* 2011;164(5):801-9.
63. Hesarghatta Shyamasunder A, Abraham P. Measuring TSH receptor antibody to influence treatment choices in Graves' disease. *Clin Endocrinol (Oxf).* 2017;86(5):652-7.

64. Okosieme OE, Lazarus JH. Current trends in antithyroid drug treatment of Graves' disease. *Expert Opin Pharmacother*. 2016;17(15):2005-17.
65. Okosieme OE, Lazarus JH. Important considerations in the management of Graves' disease in pregnant women. *Expert review of clinical immunology*. 2015;11(8):947-57.
66. Andersen SL, Olsen J, Wu CS, Laurberg P. Spontaneous abortion, stillbirth and hyperthyroidism: a danish population-based study. *Eur Thyroid J*. 2014;3(3):164-72.
67. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. *Obstetrics and gynecology*. 1994;84(6):946-9.
68. Medici M, Korevaar TI, Schalekamp-Timmermans S, Gaillard R, de Rijke YB, Visser WE, et al. Maternal early-pregnancy thyroid function is associated with subsequent hypertensive disorders of pregnancy: the generation R study. *J Clin Endocrinol Metab*. 2014;99(12):E2591-8.
69. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. *American journal of obstetrics and gynecology*. 1989;160(1):63-70.
70. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. *Obstetrics and gynecology*. 2006;107(2 Pt 1):337-41.
71. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid*. 1992;2(2):155-9.
72. Evans C, Gregory JW, Barton J, Bidder C, Gibbs J, Pryce R, et al. Transient congenital hypothyroidism due to thyroid-stimulating hormone receptor blocking antibodies: a case series. *Ann Clin Biochem*. 2011;48:386-90.
73. Bucci I, Giuliani C, Napolitano G. Thyroid-Stimulating Hormone Receptor Antibodies in Pregnancy: Clinical Relevance. *Frontiers in endocrinology*. 2017;8:137.
74. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol*. 2008;158(1):69-75.
75. Cooper DS. Antithyroid drugs. *The New England journal of medicine*. 2005;352(9):905-17.
76. Taylor PN, Vaidya B. Side effects of anti-thyroid drugs and their impact on the choice of treatment for thyrotoxicosis in pregnancy. *European Thyroid Journal*. 2012;1(3):176-85.
77. Cooper DS, Rivkees SA. Putting propylthiouracil in perspective. *J Clin Endocrinol Metab*. 2009;94(6):1881-2.

78. Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, et al. The Role of Propylthiouracil in the Management of Graves' Disease in Adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid*. 2009;19(7):673-4.
79. Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. Methimazole embryopathy: delineation of the phenotype. *Am J Med Genet*. 1999;83(1):43-6.
80. Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, et al. Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab*. 97. United States 2012. p. 2396-403.
81. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. *J Clin Endocrinol Metab*. 2013;98(11):4373-81.
82. Li H, Zheng J, Luo J, Zeng R, Feng N, Zhu N, et al. Congenital anomalies in children exposed to antithyroid drugs in-utero: a meta-analysis of cohort studies. *PloS one*. 2015;10(5):e0126610.
83. Li X, Liu GY, Ma JL, Zhou L. Risk of congenital anomalies associated with antithyroid treatment during pregnancy: a meta-analysis. *Clinics (Sao Paulo, Brazil)*. 2015;70(6):453-9.
84. Seo GH, Kim TH, Chung JH. Antithyroid Drugs and Congenital Malformations: A Nationwide Korean Cohort Study. *Ann Intern Med*. 2018.
85. Laurberg P, Andersen SL. Therapy of endocrine disease: antithyroid drug use in early pregnancy and birth defects: time windows of relative safety and high risk? *Eur J Endocrinol*. 2014;171(1):R13-20.
86. Lazarus JH. Pre-conception counselling in graves' disease. *Eur Thyroid J*. 2012;1(1):24-9.
87. Rotondi M, Cappelli C, Pirali B, Pirola I, Magri F, Fonte R, et al. The effect of pregnancy on subsequent relapse from Graves' disease after a successful course of antithyroid drug therapy. *J Clin Endocrinol Metab*. 2008;93(10):3985-8.
88. Laurberg P, Krejbjerg A, Andersen SL. Relapse following antithyroid drug therapy for Graves' hyperthyroidism. *Current opinion in endocrinology, diabetes, and obesity*. 2014;21(5):415-21.
89. Khan I, Okosieme OE, Lazarus JH. Current challenges in the pharmacological management of thyroid dysfunction in pregnancy. *Expert review of clinical pharmacology*. 2017;10(1):97-109.
90. Poppe K, Velkeniers B, Glinoeer D. Thyroid disease and female reproduction. *Clin Endocrinol (Oxf)*. 2007;66(3):309-21.

91. Cramer DW, Sluss PM, Powers RD, McShane P, Ginsburgs ES, Hornstein MD, et al. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? *Journal of assisted reproduction and genetics*. 2003;20(6):210-5.
92. Poppe K, Glinoeer D, Van Steirteghem A, Tournaye H, Devroey P, Schiettecatte J, et al. Thyroid dysfunction and autoimmunity in infertile women. *Thyroid*. 2002;12(11):997-1001.
93. Taylor PN, Okosieme OE, Premawardhana L, Lazarus JH. Should all women be screened for thyroid dysfunction in pregnancy? *Women's health (London, England)*. 2015;11(3):295-307.
94. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison S, et al. Detection of thyroid dysfunction in early pregnancy: Universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab*. 2007;92(1):203-7.
95. Dosiou C, Barnes J, Schwartz A, Negro R, Crapo L, Stagnaro-Green A. Cost-effectiveness of universal and risk-based screening for autoimmune thyroid disease in pregnant women. *J Clin Endocrinol Metab*. 2012;97(5):1536-46.
96. Chang DL, Leung AM, Braverman LE, Pearce EN. Thyroid testing during pregnancy at an academic Boston Area Medical Center. *J Clin Endocrinol Metab*. 2011;96(9):E1452-6.
97. Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. *Eur J Endocrinol*. 2012;166(1):49-54.