Review Article

Thyroid function in pregnancy

Ilaria Muller[#], Peter N. Taylor[#], John H. Lazarus

Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, Cardiff, UK

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ilaria Muller. Thyroid Research Group, Systems Immunity Research Institute, Cardiff University School of Medicine, UHW, Heath Park, Cardiff CF14 4XN, UK. Email: mulleri4@cardiff.ac.uk.

Abstract: Thyroid hormones are essential for pregnancy maintenance and correct foetal development; even a mild thyroid disturbance can cause potential adverse consequences on obstetric outcomes and foetal well-being. Pregnancy also places substantial demands on the thyroid axis, with consequent increase of thyroid hormone requirements. Thus, it is critical to maintain appropriate levels of iodine and thyroid hormones during pregnancy. Thyroid disorders are relatively common in pregnancy, and a prompt diagnosis of thyroid dysfunction requiring medical intervention is needed. Data from large population cohorts and randomised clinical trials demonstrated that it is challenging to establish precise cut-offs of thyroid dysfunction in pregnancy, and therefore diagnose milder forms of thyroid dysfunction. There is now a growing awareness of the need for greater clarity with regard to gestational thyroid reference ranges which should not only be trimester specific, but also population and laboratory method specific. Sub-optimal thyroid function might also be exacerbated by the presence of thyroid autoantibodies, especially anti-thyroid peroxidase antibodies; such evidence led to a change in the most recent American Thyroid Association guidelines. Overt thyroid dysfunction is associated with adverse outcomes, particularly foetal loss, and early gestational age at delivery; there is universal agreement about the absolute necessity to treat such conditions. On the other hand it is unclear whether marginal thyroid abnormalities, such as subclinical hypothyroidism (ScHypo) and isolated hypothyroxinemia (IH), have sufficient impact to justify widespread screening for thyroid disease in pregnancy. This has led to substantial discrepancies between societal guidelines. More recently concern has also been raised regarding over-treatment of hypothyroidism which may result in adverse neurocognitive outcomes. There is a pressing need for evidence-based studies to determine whether universal thyroid screening in pregnancy is appropriate. Iodine deficiency and endocrine disruptors are also likely to have similar deleterious impacts as thyroid insufficiency and greater clarity is also needed here.

Keywords: Thyroid; hypothyroidism; hyperthyroidism; pregnancy; screening

Received: 10 October, 2018. Accepted: 28 October, 2018.
doi: 10.21037/aot.2018.10.05
View this article at: http://dx.doi.org/10.21037/aot.2018.10.05

Introduction

When considering the importance of thyroid function in pregnancy, it is also essential to consider iodine, which is an integral component of thyroid hormone. It has been long established that severe maternal iodine deficiency has a profound deleterious impact on offspring neurodevelopment (1). Infants or children with an intelligence quotient (IQ) of 40 or less, a condition known as "cretinism", were commonly reported in severely iodine deficient areas worldwide; thanks to the introduction of iodine supplementation before and during early pregnancy, this condition can now be prevented (2).

In the last 20 years there has been a substantial increase

Table 1 Physiologic changes in pregnancy that influence thyroid function

Physiologic change	Impact on thyroid economy
↑Thyroid binding globulin (TBG)	↑Serum total T4 and T3 concentration
↑hCG levels (1st trimester)	↑Free T4 and ↓TSH (thyroidal hCG response may be impaired in TPOAb positive women)
↑Plasma volume	↑T4 and T3 pool size
↑Type III iodothyronine-deiodinase activity (inner ring deiodination) from placenta	↑T4 and T3 degradation consequent ↑demand on thyroid gland for increased hormone production
Thyroid gland enlargement (in some women)	↑Serum thyroglobulin
↑Renal iodine clearance	↑Iodine requirements; ↓hormone production in iodine deficient areas

Adapted from Lazarus (6). hCG, human chorionic gonadotrophin; TBG, thyroxine binding globulin; T3, triiodothyronine; T4, thyroxine. Up arrow (↑), increased; down arrow (↓), decreased.

in our understanding of the importance of thyroid hormones for maintaining a successful pregnancy and foetal development, especially with regard to its neurological development (3-8). In particular, there has been a growing appreciation that maternal thyroid hormone levels are especially important in the first half of pregnancy whilst the foetal thyroid is developing.

Thyroid disorders are common globally in women of child-bearing age (9); furthermore, pregnancy increases the demands on the hypothalamic-pituitary-thyroid axis. As a result thyroid dysfunction, particularly borderline thyroid abnormalities, are frequently encountered during pregnancy. Correction of both overt hypothyroidism and hyperthyroidism dramatically reduces the risk of adverse obstetric outcomes including foetal loss and preterm birth (3,6). Currently all endocrine, thyroid, and obstetrical societies recommend initiating treatment for overt thyroid disease detected in pregnancy. However, the benefits of treating more marginal thyroid function such as subclinical hypothyroidism (ScHypo) and isolated hypothyroxinemia (IH) are less clear, therefore the need of a universal screening program of thyroid function in pregnancy is still a major debate in thyroidology. Furthermore many women are established on levothyroxine either prior to or during pregnancy (10).

Thyroid physiology in pregnancy

Our understanding of the appreciable effects of pregnancy on thyroid economy has had notable advances in the last 20 years (4). Pregnancy determines an increase of urinary iodine excretion and thyroxine-binding globulin (TBG) levels, and a rise in thyroid hormone degradation by placental type III deiodinase; furthermore, the foetus utilizes maternal thyroid hormones. Thus the demands on maternal thyroid axis are increased, and as a consequence the maternal thyroid hormone production rises (3). This scenario induces compensatory mechanisms such as an increased thyroidal production of free-thyroxine (FT4) and free tri-iodothyronine (FT3) triggered by the placental secretion of human chorionic gonadotrophin (hCG) (11). Furthermore it is well known that pregnancy induces a condition of general immunosuppression for all its duration (12). As a consequence, the activity of autoimmune disorders is reduced during gestation, including thyroid autoimmunity and leading to additional changes in thyroid hormones levels.

Table 1 summarizes the significant, but reversible, changes in thyroid function occurring in pregnancy (3,5). During gestation, plasma volume and glomerular filtration rate increase significantly, with consequent augmented excretion of iodine in the urine (13). Thus the reduced serum iodine concentration exacerbates iodine deficiency, and may be causative of goitre and reduced levels of maternal thyroxine (T4), especially in areas of endemic cretinism (14). An augmented thyroid volume has been observed even in areas of mild-moderate iodine deficiency (15,16), but not in iodine sufficient regions (15). This is of particular relevance to the UK which is iodine deficient (17) and data from the UK has shown mild-moderate iodine deficiency in pregnancy is associated with a lower child IQ (18). A daily iodine intake of 250 µg in pregnancy is recommended by several different authorities (19,20), however it is not always achieved even in developed parts of the world (9,21). Endocrine disruptors may exacerbate iodine deficiency and may also have a

deleterious effect on offspring neurodevelopment (22,23). Thus, to prevent foetal brain damage additional iodine supplementation in pregnancy may be required in areas of suboptimal iodine nutrition. Ideally iodine sufficiency should be attained prior to conception by either universal salt iodisation or targeting women of child-bearing age (24).

During pregnancy the levels of thyroid hormone transport proteins rise, especially TBG, due to oestrogen-induced increase in TBG sialylation with consequent reduced degradation and increased half-life, as well as enhanced hepatic synthesis (25,26). As a consequence, total T4 and total T3 levels rise.

The hCG glycoprotein hormone shares a common alpha subunit with thyroid stimulating hormone (TSH) but has a unique beta subunit, which confers specificity; the amount and type of hCG secretion by placenta seems to be somewhat dependent on ethnicity (27). *In vitro* studies on thyroid tissue and on eukaryotic cells stably expressing the human TSH receptor (TSHR) showed that hCG acts as a TSH agonist (28); however others showed limitations of such *in vitro* assays, therefore this topic is still object of controversy (29).

The incidence of gestational transient hyperthyroxinemia caused by elevated hCG levels and therefore not treated was 0.285% in a study screening more than 23,000 pregnant women (30). There is good evidence that hyperemesis gravidarum (severe nausea and vomiting), which sometimes requires hospitalisation for the management of its potential complications including dehydration and ketosis, may be associated with hyperthyroidism due to excess hCG stimulation (31). Furthermore, both the hCG secreted in the first trimester of pregnancy and that produced by hydatidiform mole tissue, have a high thyroid stimulating specific activity (32). The sensitivity of TSHR to hCG has also been demonstrated by a few isolated case reports of familial gestational hyperthyroidism caused by mutant TSHR (missense mutation) which was more sensitive to hCG than the wild type receptor (33-35). Recent data suggests that women with positive autoantibodies to thyroid peroxidase (TPOAb) may have an impaired response to hCG (36) and therefore may not be able meet the extra demands placed on the thyroid. This may be a key factor in why TPOAb positivity is associated with adverse outcomes.

In this complex scenario the precise mechanisms leading to a decline in free thyroid hormones have not been elucidated, however the interaction of oestrogens, hCG, TSH and thyroid binding proteins is crucial. In iodine deficient areas (including marginal iodine deficiency) the pregnant woman may become significantly hypothyroxinaemic with preferential T3 secretion, especially if iron deficient (37). As a general rule, FT4 transiently rises in the first trimester due to the relatively high circulating hCG concentration, while FT4 decreases in the second and third trimester, albeit still within the normal reference range (3). Changes in FT3 concentration are also seen in which they broadly parallel the FT4, again within the normal range (3). The thyroidal 'stress' is also evidenced by a rise in the median TSH and serum thyroglobulin; in particular TSH levels have a specular trend compared with hCG, therefore lower in the first trimester and higher in the second and third trimesters (4,38).

Thyroid function assessment during pregnancy

Clinical relevance

The profound changes that occur during pregnancy have consequences for thyroid hormone serum concentrations and the assessment of thyroid function. There is a significant overlap between the signs and symptoms of the hypermetabolic state typical of normal euthyroid pregnant women, and those due to thyroid dysfunction. Therefore, a differential diagnosis can be challenging to make, and the availability of reliable accurate tests for gestational thyroid function is crucial to this purpose. However, the notable underlying physiological changes occurring during pregnancy also cause many difficulties with the laboratory measurements of thyroid function. The diagnosis of maternal gestational thyroid dysfunction is of clinical importance for both maternal and foetal health (39,40), and therefore requires (I) specialised assays measuring thyroid hormones with high specificity and sensitivity; (II) normal and reliable intervals for comparison during pregnancy; and (III) appropriate treatment regimen. To this purpose dedicated guidelines have been published by several organizations (41,42).

Several factors influence thyroid status in pregnancy, including iodine status (16), hCG levels (11), ethnicity (27,43), body mass index (44), parity (44) and male foetal sex (44). A population of pregnant women not biased by such key factors is required to calculate more precise gestational-related reference ranges for thyroid hormones, essential to make a correct diagnosis. Therefore, centres should assess their normal thyroid reference-range excluding women with thyroid dysfunction and/or positivity for TPOAb, using medications altering thyroid

function, resident in areas of iodine deficiency. Equally, women who have undergone *in vitro* fertilization or are expecting twins, since both conditions are characterised by higher hCG levels (45). The current American Thyroid Association guidelines recommend the use of pregnancy specific, local population-based reference ranges where possible (46). Furthermore, normal thyroid status changes over pregnancy, therefore the accurate assessment of thyroid function in pregnant women requires the use of different gestational age (trimester-specific) reference intervals (47).

Two guidelines provided by the Endocrine Society (42) and the National Academy of Clinical Biochemistry (41) detailed the strengths and limitations of currently available thyroid function tests. TSH has been traditionally the primary marker of thyroid status during pregnancy, however the measurement of T4 levels is essential in differentiating between overt and subclinical thyroid disease, and the assessment of thyroid hormones during pregnancy has several weaknesses. In particular the free hormone assays based on measuring the concentrations of thyroid hormone binding-proteins are known to be method-dependent, and therefore are at risk of providing inaccurate FT4 and FT3 values during gestation. Direct FT4/FT3 assays based on equilibrium dialysis are more reliable however less available since expensive and time-consuming (48). Finally, most laboratories still do not use pregnancy-specific reference intervals for thyroid function tests.

In some cases, serum TPOAb and autoantibodies to thyroglobulin (TgAb) and/or to TSHR (TRAb) can provide other information. TPOAb can predict the risk of hypothyroidism; low TSH levels in pregnant women are accompanied by TRAb in 60–70% of the cases, and need to be monitored since may cause foetal and neonatal hyperthyroidism (46).

TSH measurement

Since TSH and FT4 are linked by a log-linear relationship, very small changes in T4 levels will determine a much larger variation in serum TSH concentrations (49,50). For this reason serum TSH levels represent the first biochemical indicator checked in the suspect of thyroid dysfunction. However during gestation thyroid and pituitary functions undergo notable variations; for example during early pregnancy the significant rise in hCG concentrations determines a suppression of TSH levels by 20–50% by week 10 (51). Therefore, the measurement of only serum TSH in women treated for thyroid dysfunction during gestation has several limitations since can result in maternal under-replacement with levothyroxine, or overtreatment with anti-thyroid drugs (ATD), both scenarios causing maternal hypothyroidism with consequent increased risk for impaired foetal brain development. The biochemical evaluation of the hypermetabolic symptoms presented by women with reduced TSH but still normal FT4 levels may include the measurement of FT3 and FT3 index (FT3I).

Total and free thyroid hormone measurements

T4 and T3 circulates >99% bound to plasma transport proteins, mainly to TBG and to a lesser extent to transthyretin and albumin; the free- and protein-bound hormones are at equilibrium (52). The highly concentrated (nanomolar) protein-bound hormone fractions act as a storage reservoir and prevent thyroid hormones from entering cells where they exert their biological effects. The biologically active form of thyroid hormones is that free from protein-binding, and present at much lower concentrations (picomolar) (53).

Assays for total thyroid hormones have been much easier to develop compared with their free component, due to their increased serum concentrations, and are considered more accurate and valid compared with free hormone assays. In particular total T4 assays generally agree quite well, and are characterised by better defined reference intervals in adults (54). However, in pregnancy oestrogens cause an increase of TBG levels and therefore a consequent increase of total T4 concentrations (up to 1.5-fold in the second trimester), thus gestation-specific reference intervals for total thyroid hormones are necessary for accuracy (6). Due to the influence of thyroid hormone binding proteins, in most clinical laboratories FT4 assays have replaced the total T4 testing.

The measurement of the free quote of thyroid hormones allows taking into account the biologically active form only, and this is a clear advantage. However, this approach has significant challenges compared with the total thyroid hormone assays due to: (I) the lower concentration of analyte; (II) the risk to disturb the equilibrium between the free and protein-bound hormone quotes; (III) the potential interference of the much higher concentrations of the protein-bound hormone quote. In fact due to the changes in the TBG concentrations during pregnancy, concern has been raised regarding the accuracy of FT4 assays (54). It has to be noted that such interference is maximum in the third trimester, while minimal in the first trimester, which

is the most important time-point for thyroid dysfunction screening. Furthermore, variation in FT4 as opposed to T4 levels is more robustly associated with adverse obstetric and offspring outcomes (55,56).

The first step in the measurement of the free hormones is their physical separation from the protein bound hormones by specific techniques (i.e., equilibrium dialysis or ultrafiltration), followed by immunoassay, or more recently using isotope dilution mass spectrometry (MS) (57-59). The immunoassay methodologies are more prone to interference by thyroxine binding protein abnormalities or immunoglobulins (i.e., heterophilic antibodies and antibodies to thyroid hormones) (60-62). Possible strategies to overcome this limitation are: (I) to measure the total hormone concentrations (T3 and T4) correcting for the increased binding proteins, i.e., directly measuring the TBG levels to provide T4/TBG or T3/TBG ratios; (II) to perform a T3 or T4 uptake test to estimate free thyroid hormone indices (63-67).

More recently free thyroid hormones have been measured by tandem MS which provides more accurate, specific, fast and simple measurements (68-70). Further development was achieved coupling MS with high performance liquid chromatography (62).

These assays are complex and laborious, therefore often not routinely employed in clinical practice and limited to specialized laboratories. In fact, clinical laboratories prefer to use commercially available immunoassays for FT4 and FT3 only estimating the concentration of the free thyroid hormone quote, since not physical separating that from the protein-bound hormone quote (71). Surprisingly, one of the commercially available FT4 assays resulted to correlate more closely to total T4 assays than to FT4 measured following physical separation of the free-quote from binding proteins (72). However the physiological increase in TBG levels occurring during gestation has been showed to influence at various extents the results obtained with commercial FT4 immunoassays (73). This explains why a significant method-dependent variation exists when measuring gestational FT4 levels, with different groups reporting serum concentration of thyroid hormones to be decreased, increased or unchanged during pregnancy depending on the assays used; thus it is challenging to establish universal gestation-related FT4 reference intervals (60,61).

Considering the differences in thyroid hormones related to the laboratory method used and the gestation period, the use of method- and gestation-specific reference intervals is recommended for the correct interpretation of thyroid function in pregnant women (71). Method- and gestation-specific reference intervals for FT4 should be derived in the appropriate reference populations. To this purpose both the iodine and thyroid autoimmunity status should be evaluated when selecting the reference population; only iodine sufficient subjects should be taken into account (41,42). Unfortunately, very few FT4 immunoassay manufacturers include appropriate method-specific normal pregnancy-related reference intervals, and most clinical laboratory reports only provide reference intervals not adjusted for gestation, making challenging the interpretation of laboratory results during pregnancy. In cases where a clear diagnosis is difficult to reach, the integration of both free and total thyroid hormone assays, and/or reanalysis of the samples on a different platform are possible options to consider.

Trimester- and method-specific reference intervals

In order to reduce the global variability of thyroid hormone assessments, numerous trimester-specific population-based reference intervals have been derived. In 2010 Lazarus *et al.* provided a comprehensive summary of some trimester-specific reference ranges for different populations worldwide (5). In 2017 Korevaar *et al.* reported additional updated worldwide reference ranges for early pregnancy in their supplementary Table S1 (8).

Current T4 and TSH levels are affected worldwide by iodine deficiency, ranging from mild to moderate and still present in some geographical areas despite the national policies of iodine implementation using mandatory iodized salt. Furthermore, the overall iodine intake may be significantly different due to the variable content of natural iodine within the local food and water, or the presence of variable individual responses to supplementation (5). In the first trimester we assist to an increase of total thyroid hormone concentration, with consequent decrease of both FT4 and TSH. In areas of iodine sufficiency the second and third trimesters are characterised by increased TSH levels, while FT4 and FT3 levels decrease; this is not the case in iodine deficient populations due to the TSH stimulation (5). As previously highlighted the interpretation of gestational FT4 values needs caution to avoid misinterpretation, since the results of FT4 laboratory assays are characterised by significant variability even within the same population (60,61).

It should be noted that the measurements by different methods in distinct populations did provide very dissimilar

Table 2 Physiology of thyroid hormone availability to foetal brain

(A) Before onset of foetal thyroid function (1st trimester)
T4 and T3 are present in embryonic and foetal fluids and tissues
T4 and T3 are of maternal origin
Nuclear receptors are present and occupied by T3
D2 and D3 are expressed in brain
(B) Between onset of foetal thyroid function and birth (2nd–3rd trimesters)
Maternal transfer of T4 and T3 continues
Brain T3 is dependent on T4 and D2 and not on systemic T3
Normal maternal T4 protects foetal brain from T3 deficiency
Normal T3 in low T4 mother does not prevent cerebral T3 deficiency

Adapted from Lazarus *et al.* (5). D2, iodothyronine-deiodinase type II; D3, iodothyronine-deiodinase type III; T3, triiodothyronine; T4, thyroxine.

ranges; furthermore slightly divergent results were produced even in the same population in case of different ethnicities, and the same method applied to different populations provided significantly different results (5). As additional point, the population-based reference ranges did not take into account the various genetic set-points specific for every subject (74,75). Similarly, gestational specific reference intervals may be more affected by intra-individual changes than specific single measurements. In fact the use of gestation- and method-specific reference intervals, even if determining a crucial reduction in results variability and risk of misinterpretation, should not prevent from considering also the intra-individual variability (5).

In conclusion, a correct interpretation and comparison of gestation-specific results should always consider the assay analysis methods used, the size of the group evaluated, the subject inclusion and exclusion criteria including the iodine, ethnicity, age and singleton pregnancy status, the study design (cross-sectional or longitudinal) and the statistical methods used for data analysis.

Epidemiology of thyroid disease in pregnancy

Overt maternal hypothyroidism—elevated TSH and low maternal FT4 concentrations—occurs in approximately 0.2–0.6% of pregnant women (76,77), whereas ScHypo—elevated TSH and normal FT4 concentrations—can occur in up to 18% of pregnancies depending on the precise definition and TSH cut-point used (8,46). IH is defined as a normal TSH with FT4 below the 2.5 percentile, and was originally considered to be a pregnancy specific condition possibly arising as a consequence of mild iodine deficiency. This concept has been more recently challenged as it occurs in iodine sufficient areas and does not typically resolve with iodine supplementation (78,79). Other factors including elevated BMI, older age, iron status and placental angiogenic factors have all been identified as likely risk factors for IH (80-82).

Pathological overt hyperthyroidism, usually due to Graves' disease, occurs with a frequency of approximately 0.2% (83), however previously treated maternal Graves' disease prior to pregnancy is more common and can occur prior to 1% of pregnancies (83). New onset pathological hyperthyroidism during pregnancy is much rarer with a prevalence of 0.05% for Graves' disease (83). Gestational thyrotoxicosis (suppressed TSH and elevated FT4) mainly through excess hCG and usually associated with hyperemesis gravidarum, occurs in up to 3% of pregnancies (83). Subclinical hyperthyroidism (ScHyper) most commonly occurs as a result of peak hCG levels (44) although may occur due to pathological thyroid disease. Owing to this dual cause of ScHyper its true consequences and prevalence are poorly studied.

Consequences of maternal thyroid dysfunction

There is good evidence that maternal thyroid dysfunction during pregnancy may affect the obstetric outcome, as well as maternal and foetal health (4,6,8,39,40).

Table 2 summarises the impact of maternal thyroid hormones on foetal brain during different stages of pregnancy (5,84).

Overt hypothyroidism

Overt hypothyroidism has been repeatedly associated with a higher risk of adverse obstetric outcomes including foetal loss, premature delivery, low birth weight and preeclampsia (76,85). Effects have been observed on foetal neurodevelopment; a large case-control study demonstrated children born to women with untreated hypothyroidism had a 7-point lower IQ than women with normal thyroid function (86).

ScHypo

ScHypo is also associated with similar adverse obstetric

outcomes as overt hypothyroidism, albeit with a more modest effect. Studies have demonstrated an increased incidence of adverse pregnancy outcomes including preterm delivery, placental abruption, respiratory distress, early pregnancy loss and admissions to the intensive care unit (87-91) but it has not been associated with impaired development of offspring (92-94).

IH

Although IH is also regarded as a mild form of thyroid failure, it has been found to be associated with impaired offspring developmental outcomes (7), but not obstetric outcomes in stark contrast to ScHypo. In particular, adverse consequences have been observed regarding offspring verbal delay (95). The relationship between maternal FT4 and offspring IQ appears to be "U" shaped with individuals with hypothyroxinemia having lower IQ, and lower grey matter and cortical volume (7). Maternal IH has also been shown to be associated with offspring autism (96) and attention-deficit/hyperactivity disorder (ADHD) (97,98).

TPOAb positivity

TPOAb positivity is a major risk factor for ScHypo (99). However, the combination of ScHypo and TPOAb positivity appears to have a synergistically adverse outcome. In particular, adverse synergistic associations occur for miscarriage, premature delivery and gestational diabetes mellitus (100). It also appears to be a risk factor in its own right for miscarriage and pre-term delivery (101).

Pathological hyperthyroidism

Pathological hyperthyroidism is a condition independent from hCG levels, and usually determined by Graves' disease or, more rarely, by an autonomous production of thyroid hormones (i.e., toxic goitre or adenoma). It is associated with increased risk of maternal heart failure, preeclampsia, foetal loss, pre-term birth and low birth weight (83,102,103).

Given that all endocrine and obstetric guidelines endorse the treatment of pathological thyroid dysfunction, it is difficult to ascertain from current studies which of these negative outcomes are secondary to the maternal thyroid dysfunction itself, or foetal hyperthyroidism (due to TRAb crossing the placenta), or consequences of treating the maternal thyrotoxicosis, including ATD side effects or induced foetal hypothyroidism (8).

Gestational hyperthyroidism and ScHyper

Gestational hyperthyroidism is a usually transient condition caused by increased hCG levels during the first trimester of pregnancy, determining an augmentation of thyroid hormone production. It is usually responsible for the majority of ScHyper cases diagnosed in pregnancy and is considered to be a non-pathological condition (8).

There is a current lack of data investigating the effects of pathological ScHyper on adverse pregnancy, maternal, foetal and neonatal outcomes; one first difficulty is to reliably distinguish cases of pathological versus non-pathological (gestational) ScHyper (8). This step is crucial, since recent findings showed that increased levels of thyroid hormones did not represent a risk factor for preeclampsia if associated with high hCG levels (indicating gestational hyperthyroidism), while a 3.4–11.1-fold higher risk of such adverse outcome was present if they were associated with low hCG levels (indicating pathological hyperthyroidism) (104). A combined measurement of thyroid function and hCG would therefore help in distinguishing these two forms of ScHyper in pregnancy.

Benefits of treatment of maternal thyroid dysfunction

Treatment of overt hypothyroidism

Although no randomised controlled trials of levothyroxine for overt hypothyroidism in pregnancy have been conducted, the wealth of data regarding the adverse consequences of overt hypothyroidism with pregnancy effects mean performing such studies would be unethical. However, all endocrine and obstetric society guidelines recommend treatment of overt hypothyroidism in pregnancy; in women established on levothyroxine prior to pregnancy dose adjustments are often needed to cope with the increased thyroidal demand (8,46).

Despite this, many women on levothyroxine have sub-optimal thyroid function during pregnancy and in those with TSH levels >4.5 mU/L an increased risk of foetal loss has been described (105). The "U" shaped response seen with maternal thyroid function and IQ (7) and the CATS II study (94,106) also shows that caution should be taken in not over-treating patients with hypothyroidism or ScHypo. This is particularly important in treating women with milder thyroid abnormalities as the residual function in the thyroid gland may be readily responsive to hCG resulting in over-treatment if injudicious doses of levothyroxine are given.

Box 1 Management of hypothyroidism in pregnancy

Preconception: optimize levothyroxine therapy in patients with pre-existing disease, warning them of the need to increase dose over pregnancy and the need for closer monitoring
On confirmation of pregnancy, increase dose by 30–50% of preconception dose. Dose requirement is often higher in post-ablative and post-surgical hypothyroidism
If newly diagnosed overt hypothyroidism in pregnancy, start pregnancy-specific body weight-based dose: 2 mcg/kg/day
Be aware of drug interactions:
(I) Drugs which impair thyroxine absorption: iron supplements, cholestyramine, calcium carbonate, soy milk
(II) Drugs which increase thyroxine clearance: carbamazepine, rifampicin, valproate
Check thyroid function early in first trimester and every 4–6 weeks
Aim for TSH <2.5 mU/L in the first trimester and <3 mU/L in later pregnancy. Take care to avoid a T4 level that is too high—aim for upper half of the reference-range
After delivery reduce levothyroxine to preconception dose
Recheck thyroid function at 6 weeks postpartum

Adapted from Lazarus (6).

Box 1 reports a clinical algorithm for the correct management of hypothyroidism in pregnancy (8,42).

Treatment of ScHypo and IH

To date three large randomized controlled trials have investigated the effects of screening and treating borderline low thyroid function in pregnancy: the controlled antenatal thyroid screening (CATS) study (92), a study by Casey *et al.* (93), and a recent study by Nazarpour *et al.* (107), summarized in *Table 3*.

In terms of offspring benefits, neither CATS nor Casey study showed any beneficial effects of treatment on children IQ. Reasons for negative findings might include relatively late initiation of treatment (particularly in the Casey study) (93) and early age of IQ assessment (particularly in the CATS study) (92). Follow on analysis of the CATS study (CATS II) confirmed no apparent benefit of treatment at age 9 (94) although identified levothyroxine over-treatment may increase the risk of ADHD (106).

In terms of pregnancy outcomes, no benefit was observed with levothyroxine on obstetric outcomes in both the Casey (93) and the Nazarpour study (107), as well as in a meta-analysis of the two studies considering five obstetrical and neonatal outcomes: preterm delivery <37 weeks gestation, gestational age at delivery, placental abruption, neonatal intensive care admission and head circumference (108). A more recent analysis using data linkage and the majority of the CATS cohort identified that levothyroxine treatment significantly reduced the risk of miscarriage/still birth (109). This was in agreement with previous findings from another prospective study identifying that levothyroxine reduced the risk of miscarriage and preterm birth (110).

Treatment of pathological hyperthyroidism

The treatment of hyperthyroidism in pregnancy is imperative due to its important negative effects on pregnancy outcome and both mother and foetus health (83,102,103). Thus no randomized controlled trials have been conducted in pregnant hyperthyroid women comparing ATD interventions with no interventions (111).

ATD are the preferred treatment during pregnancy (46,112) since radioiodine is absolutely contra-indicated due to deleterious effects on foetal thyroid gland and teratogenicity (113-115), and thyroidectomy in pregnancy results in increased morbidity compared to non-pregnant women (116). Thyroidectomy can be considered in special circumstances during pregnancy, such as allergy/contraindications to ATD or if euthyroidism cannot be achieved despite high doses. Thyroidectomy if required should be performed in the second trimester.

All ATD cross the placenta and therefore the lowest possible dose to control hyperthyroidism is recommended (46,76). The most used ATD are carbimazole (CBZ)/methimazole (MMI) and propylthiouracil (PTU), and it is still unclear whether there is a substantial difference in

Table 3 Summary of the CATS, Casey and Nazarpour studies

	CATS study [2012]	Casey study [2017]	Nazarpour study [2018]
Countries	UK, Italy	USA	Iran
Placebo-controlled	No	Yes	No
N randomised	794	677	366
Maternal age (y: mean ± SD)	30±5.4; controls 31±5.3	27.7±5.7; controls 27.3±5.7	27.0±5.3; controls 26.9±4.7
Gestational age at recruitment (weeks)	[median (IQR)]*, 12.3 (11.6–13.6); controls 12.3 (11.6–13.5)	(mean ± SD)#, 16.6±3.0; controls 16.7±3.0	(mean ± SD)^, 11.4±4.1; controls 12.2±4.3
Baseline TSH (mU/L) (median)	UK 3.8 (IQR 1.5–4.7); controls 3.2 (IQR 1.2–4.2). Italy 3.1 (IQR 1.3–4.0); controls 2.4 (IQR 1.3–3.9)	4.5 (95% CI, 4.4–4.7); controls 4.3 (95% CI, 4.2–4.5)	3.8 (IQR 2.8–4.8); controls 3.6 (IQR 3.1–4.2)
Clinical outcomes	Offspring IQ (age 3 y)	Pregnancy outcomes; offspring IQ (age 5 y); offspring behaviour (age 3–5 y); offspring Bayley-III score (age 1–2 y); offspring DAS-II score (age 3 y)	Pregnancy outcomes

*, at screening; #, at randomisation; ^, at first visit. y, years; DAS, differential ability score; IQR, interquartile range; SD, standard deviation; 95% CI, 95% confidence interval.

placental transfer between them; the choice of ATD used is therefore based on side effects. CBZ/MMI have been considered for years to be associated with an increased risk of embryopathy than PTU (113). Thus considering that the teratogenic risk is greater in early pregnancy, and that PTU is associated with increased risk of maternal hepatotoxicity (117), guidelines advise to use PTU in the first trimester, and then switch to CBZ/MMI (42,118). However more recent evidence suggests a similar rate of malformations occurring with both CBZ/MMI and PTU, even if slightly lower with PTU, and no benefits derived from switching from CBZ/MMI to PTU during the first trimester (119). These observations therefore question the clinical utility of drug switch in early pregnancy, and underline the necessity to identify new ATD drugs with reduced or absent side effects.

To reduce unnecessary exposure to ATD in early pregnancy ideally all potentially fertile women should be given written instructions to (I) perform a pregnancy test within a few days after the 1st day of a missed (or atypical week) menstrual period, if pregnancy is a possibility; (II) if the pregnancy test is positive promptly contact physician/specialist nurse and do not take further ATD until advice given. Considering the risks of hyperthyroidism on one side, and those derived from ATD interventions to the other, some authors suggest that fertile women affected with hyperthyroidism and seeking pregnancy should plan thyroid surgery or radioactive iodine before the plan to become pregnant (111,118).

TRAb can cross the placenta especially during the second half of pregnancy, therefore can trigger foetal and neonatal hyperthyroidism, with deleterious consequences including but not limited to intrauterine growth retardation, craniosynostosis and death (120). Thus, women affected with Graves' disease (both current and past) and women previously treated by either thyroid surgery or radioiodine should have their serum TRAb levels measured early in pregnancy to mitigate foetal and neonatal morbidity and mortality (46). If positive, and especially if elevated, TRAb should be measured again at weeks 18–22 and in the last trimester (30–34 weeks); if still positive, appropriate neonatal and postnatal monitoring should be performed, and ATD treatment given if necessary.

The management of pathological hyperthyroidism secondary to Graves' disease is summarized in *Box 2*.

Treatment of transient gestational thyrotoxicosis and ScHyper

Transient gestational thyrotoxicosis usually occurs during the first trimester of pregnancy, and spontaneously resolves when hCG levels decrease, therefore ATD interventions are not indicated, while beta-blockers may be considered in symptomatic cases (111,121). Similarly, no ATD treatment is required for women with hyperemesis gravidarum; however, they need careful electrolyte monitoring and may

Box 2 Management of Graves' hyperthyroidism in pregnancy

Discuss with patient the need for ATD treatment, including advice on the effect on the patient, foetus and implications for breastfeeding
Ideally use propylthiouracil for the first trimester; consider stopping ATD if possible at this stage, or switching to carbimazole/methimazole although some clinicians choose to continue propylthiouracil
Monitor thyroid function regularly throughout gestation (4–6 weeks), adjusting ATD dose if necessary
Render patient euthyroid up to and during labour
Serial ultrasonography of the foetus
Check TRAbs at 30–34 weeks and inform pediatrician if TRAb positive
Check infant for thyroid dysfunction if indicated
Review postpartum—check for exacerbation and advise about breastfeeding if still on ATD

Adapted from Lazarus (6). ATD, anti-thyroid drugs; TRAb, TSHR antibody.

Table 4 Summary of consequences of abnormal thyroid function and potential treatment benefits

Thyroid dysfunction	Obstetric outcomes			Offspring neurological development		
	Effect	Impact of treatment	Comment	Effect	Impact of treatment	Comment
Overt hypothyroidism	−−	++		−−	++	
Subclinical hypothyroidism	–	?	Data for benefit are mixed. May require relatively early treatment for clear benefit	?	?	No apparent benefit
Isolated hypothyroxinemia	?	?	Lack of studies	–	?	Unclear benefit
Overt pathological hyperthyroidism	−−	++		–	+	Studied in less detail than obstetric outcomes
Subclinical hyperthyroidism	?	?	Lack of studies	?	?	Lack of studies

–, moderately adverse; −−, strongly adverse; +, moderately beneficial; ++, strongly beneficial; question mark (?), unclear.

require intravenous fluids, especially in severe forms.

ScHyper during pregnancy is usually determined by transient gestational thyrotoxicosis, therefore non-pathological and not requiring ATD treatment. Due to the difficulty to distinguish between pathological and gestational ScHyper, so far, no studies have investigated and compared the benefits, as well as the potential arms due to the drugs' side effects, of treating pathological ScHyper with ATD (8). Even a mild increase of maternal FT4 levels during pregnancy was found to be associated with preeclampsia (104), reduced birth weight (8), reduced child neurocognition (7) and increased ADHD disorder (106), however it is unlikely that the benefits of ATD treatment would overcome its risks (8).

The consequences of thyroid disease and benefits of treatment are summarized in *Table 4*.

Universal thyroid screening in pregnancy

Universal thyroid screening in pregnancy is a key debate in thyroidology. As we have indicated thyroid dysfunction is common in pregnancy and has substantial adverse implications. Furthermore, it is readily detectable and can be inexpensively treated. However, as subclinical thyroid disease and IH represent the vast majority of the thyroid abnormalities, and the benefits of treatment here are less clear, screening is therefore contentious. Nevertheless universal thyroid screening in pregnancy appears to be very cost-effective; screening solely for overt hypothyroidism also had a cost-effectiveness ratio of $6,776/QALY (quality adjusted life-year) (122) which is favourable compared to gestational diabetes mellitus screening ($12,078/QALY) and is well below the $50,000/QALY figure used in the United

States as a criteria for screening decisions.

Taken together, it is widely accepted that thyroid dysfunction is an important health problem especially in pregnancy (123). Accepted, effective and well-established treatments are available, as is the ability to readily and easily make a diagnosis. Furthermore, thyroid function testing is universally suitable to patients. For hypothyroidism, but to a lesser extent hyperthyroidism, there is a well-recognised asymptomatic stage. The natural history of subclinical thyroid dysfunction leading to overt disease is well understood, although many women with ScHypo will not progress to overt hypothyroidism if left untreated. Universal thyroid screening is cost effective even if only overt thyroid disease is considered and the nature of screening in pregnancy ensures it will be a continuous process. Thus universal thyroid screening in pregnancy meets almost all the criterion laid out by Wilson and Jungner (124). A key criterion is not resolved as there is not an agreed policy on whom to treat given the debate regarding management and treatment thresholds of IH and subclinical thyroid dysfunction. This can only be resolved by further appropriately powered randomised controlled trials.

Conclusions

In the last decade in particular, our knowledge regarding the diagnosis and treatment of thyroid disease in pregnancy has been revolutionised by substantial advances. In particular we reached a better understanding of the thyroid hormone physiology during pregnancy and the gestational-derived stress on the thyroid, which is exacerbated in areas of iodine deficiency. Furthermore, new developments have been achieved in the technology for thyroid hormone analysis, and progress has been made in defining pregnancy-specific reference intervals for thyroid hormones. In fact, the variation in assay methodology, and other determinants of thyroid function, indicated the necessity of establishing normative gestational-related (trimester-specific) reference ranges for thyroid hormones which are locally derived, namely method- and instrument-specific for the particular laboratory where samples were tested, and generated in iodine sufficient populations excluding women positive for TPOAb. This is crucial to prevent misinterpretation of thyroid function test results during pregnancy.

There is growing evidence that TPOAb positivity and higher TSH levels synergistically interact to increase the risk of adverse pregnancy outcomes. Even modest abnormalities in FT4 levels as seen in IH are also associated with adverse neurological development in offspring further supporting the role of thyroid hormone in foetal neurodevelopment. These findings would support the use of thyroid screening in pregnancy, although more data are needed.

Hypothyroidism is common in pregnancy and should be appropriately treated to reduce obstetric and foetal complications. Given foetal brain development requires adequate thyroxine delivery to foetal neurones, it also seems reasonable to treat mothers with hypothyroidism with levothyroxine to prevent IQ decrement as well as for obstetric reasons. Women already receiving levothyroxine require an increase in dose during gestation aiming for the top of the FT4 reference-range, however caution is needed to avoid over-treatment and potentially modest deleterious effects on behaviour.

Hyperthyroidism in pregnancy, usually due to Graves' disease, is uncommon but has deleterious effects on mother and foetus and requires therapy. Especially in early pregnancy treatment with ATD may increase the risk of foetal abnormalities, although treatment is safer than uncontrolled thyrotoxicosis. Use of the lowest dose of ATD possible, including consideration of temporary cessation of treatment during critical periods of organogenesis with close monitoring, will mitigate this risk. Subclinical and mild forms of hyperthyroidism are usually caused by gestational thyrotoxicosis, a non-pathological condition usually self-limiting and not requiring treatment with ATD.

Further prospective trials of early screening of thyroid function in pregnancy with both obstetric and developmental outcomes are still required to clarify whether universal thyroid screening in pregnancy is necessary. In the meantime, the correction of worldwide iodine deficiency continues to be required and monitored, and the impact of endocrine disruptors needs further exploration.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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doi: 10.21037/aot.2018.10.05
Cite this article as: Muller I, Taylor PN, Lazarus JH. Thyroid function in pregnancy. Ann Thyroid 2018.

