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THYROID FUNCTION IN PREGNANCY: MATERNAL AND FETAL OUTCOMES WITH HYPOTHYROIDISM AND SUBCLINICAL THYROID DYSFUNCTION

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INTRODUCTION

Thyroid hormones are important in the development of the fetus and the placenta as well as in maintaining maternal wellbeing. Thyroid disorders are common in the population as a whole, particularly in women, and therefore are common during pregnancy and the puerperium. Biochemical derangement of thyroid function tests are present in approximately 2.5–5% of pregnant women.[1]

Both hypothyroidism and hyperthyroidism have been associated with adverse pregnancy and neonatal outcomes. These outcomes are postulated to be mediated particularly through abnormal development of the uteroplacental unit and fetal central nervous system. This review highlights the fetal and maternal outcomes in pregnant patients with thyroid dysfunction and current thinking of how these should be managed. A multidisciplinary approach is required between obstetricians, endocrinologists, neonatologists, midwives and health visitors.

THYROID ANATOMY AND PHYSIOLOGY

The adult thyroid gland weighs 20g and consists of two lobes connected by an isthmus. It is closely attached to the thyroid cartilage and the upper end of the trachea. Embryologically it originates from the base of the tongue and descends to the middle of the neck. The thyroid has a rich blood supply from the superior thyroid (derived from the external carotid) and inferior thyroid (derived from the subclavian artery) arteries.

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Thyroid hormones are synthesised in the gland. Iodide is actively taken up into the follicular cells by the iodide pump (sodium iodide symporter) and is converted to iodine. Tyrosine becomes coupled to form pre-thyroglobulin which becomes iodinated to iodoprethyroglobulin. Coupling of T1 (monoiodothyronine) and T2 (diiodothyronine) combine to form T3 (triiodothyronine) and T4 (thyroxine), which are stored in the colloid.[2] Thyroid hormones are secreted in response to the binding of TSH (thyrotrophin) to a trans-membrane receptor linked to a G-protein second messenger system. Proportionally, more T4 than T3 is released into the circulation in a ratio of about 4:1. However, T4 is converted to the active ligand, T3, by peripheral tissues. In plasma, more than 99% of all T3 and T4 are bound to hormone binding proteins. Only the free unbound hormones are available for cellular uptake.

The thyroid gland is the first endocrine gland to develop in the fetus. It begins development 24 days after fertilisation. The thyroid consists of follicles lined by the cuboidal epithelioid cells and actively accumulates iodide from 11 weeks of pregnancy but only begins secreting thyroid hormones from about 18 weeks of gestation.[3]

However, both total and free T4 and T3 have been found and quantified in the coelomic and amniotic fluids from as early as 4 weeks post conception, and thus have to be of maternal origin.[4] Maternal T4 is thought to be the primary thyroid hormone metabolite transported across the placenta, as T4 concentrations in the extra-embryonic fluids, fetal circulation and tissues are positively correlated with maternal plasma levels prior to the onset of endogenous fetal thyroid hormone production.[4–6] Hence the availability of thyroid hormones in the fetus is primarily determined by maternal circulating levels of T4.

Maternal to fetal thyroid hormone transfer is thought to be most critical before the onset of fetal thyroid hormone production since thyroid hormones are required for normal early fetal development, especially the central nervous system. However, the analysis of cord blood from fetuses with congenital thyroid agenesis (athyreotic) at term show T4 concentrations of 25–50% of a normal term fetus, which confirms that the transfer of maternal thyroid hormones to the fetus occurs in late gestation.[7] This suggests that maternal thyroid hormones continues to be transferred throughout gestation and continues to have a role even following the onset of thyroid hormone production by the fetus. Further support of this notion comes from findings in premature neonates. They demonstrate lower circulating thyroid hormones compared to in-utero fetuses of the same gestational age. This is likely due to the abrupt loss of maternal thyroid hormone and iodide transfer for the fetus. Some have postulated that this lack of thyroid hormone in premature neonates may be a contributory factor to poor neurodevelopment outcomes.[8]

THYROID HORMONES AND PLACENTAL DEVELOPMENT

During the first trimester the human conceptus is surrounded by the placenta. The primary barrier to exchange between mother and fetus is the syncytotrophoblast layer of the placental chorionic villi which has effective tight junctions and prevents the free diffusion of thyroid hormones across it.

The human placenta in addition to this cellular barrier also regulates the amounts of thyroid hormones passing from the mother to the fetus through its expression of placental thyroid hormone transporters, thyroid hormone binding proteins, iodothyronine deiodinases, sulfotransferases and sulfatases.[9] This placental barrier also maintains a different circulating composition of thyroid hormone metabolites in the fetus compared to that in the mother.

Fetal circulating concentrations of total T3 are at least 10 fold lower than total T4. Unlike adults, the proportion of free unbound T4 is also higher than bound T4 in early gestation. Free T4 levels are determined by the fetal concentrations of the thyroid hormone binding proteins in the circulation and coelomic cavity and the amount of maternal T4 crossing the placenta. The concentration of free T4 in the coelomic fluid in the first trimester is approximately 50% of that found in the maternal circulation and could therefore exert biological effects in fetal tissues.[4]

Fetal serum is also rich in the classically-considered inactive metabolites of thyroid hormones such as sulphated thyroxine (T4S) and tri-iodothyronine (T3S), and reverse T3 (rT3).[10] Sulphated iodothyronines can be reactivated by arylsulfatases expressed in tissues locally, such as in fetal liver and brain.[11] These inactive metabolites form a circulating reservoir of thyroid hormones that can only be utilized by tissues possessing the necessary metabolic apparatus for reactivation whilst protecting other organs from excessive hormone exposure. There is now, however, increasing evidence that such "inactive" metabolites may actually have biological activity during the course of development and in adulthood. For example, T4 and rT3, but not T3, have been shown to have non-genomic actions and are able to initiate F-actin polymerisation in astrocytes and promote migration of cerebellar neurites as well as restore microfilament organisation in the cerebellum of 14 day old hypothyroid rat pups.[12]

Deiodinases are integral membrane proteins located on the plasma membrane or endoplasmic reticulum. Deiodinases act as pre-receptor regulators of thyroid hormone activity. The human placenta expresses iodothyronine deiodinases type II (D2) (which activates T4 to T3) and type III (D3) (which inactivates T4 and T3). The principle subtype in the placenta is D3, having 200 times the activity of D2. D3 effectively metabolises most of the maternal T4 presented to the placenta.[13] However, a physiologically relevant amount of T4 is transferred to the fetus. Both D2 and D3 activity per gram of placenta decrease with advancing gestation (Figure 1).[14]

Placental thyroid hormone transporters are plasma membrane proteins which facilitate cellular entry and exit of thyroid hormones. A range of transporters including monocarboxylate transporters (MCT) 8 and 10, system-L amnio acid transporters (LAT1 and LAT2) and organic anion transporting polypeptides (OATP) 1A2 and 4A1 have been located at the apical and basolateral membranes of the syncytiotrophoblasts which could facilitate thyroid hormone transfer across the cell barrier from the mother to the fetus.[15] (Figure 2)

In addition to the regulation of transplacental thyroid hormone transfer for fetal development, human placental development is itself responsive to thyroid hormone from early in gestation with evidence of expression of thyroid hormone receptors

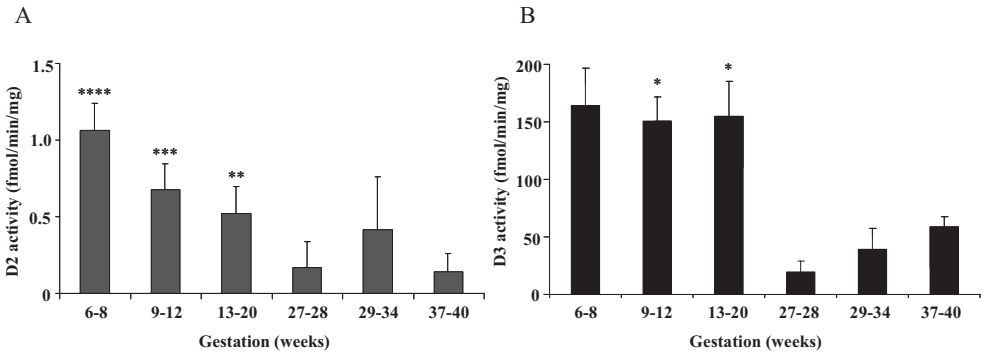

Figure 1 Iodothyronine deiodinase type 2 (A) and type 3 (B) activities in human villous placental biopsies from normal pregnancies at 6 to 34 weeks of gestation compared to term [mean (± SE) enzyme activity] $^{*}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ compared with term. (Adapted from Chan[14] with permission)

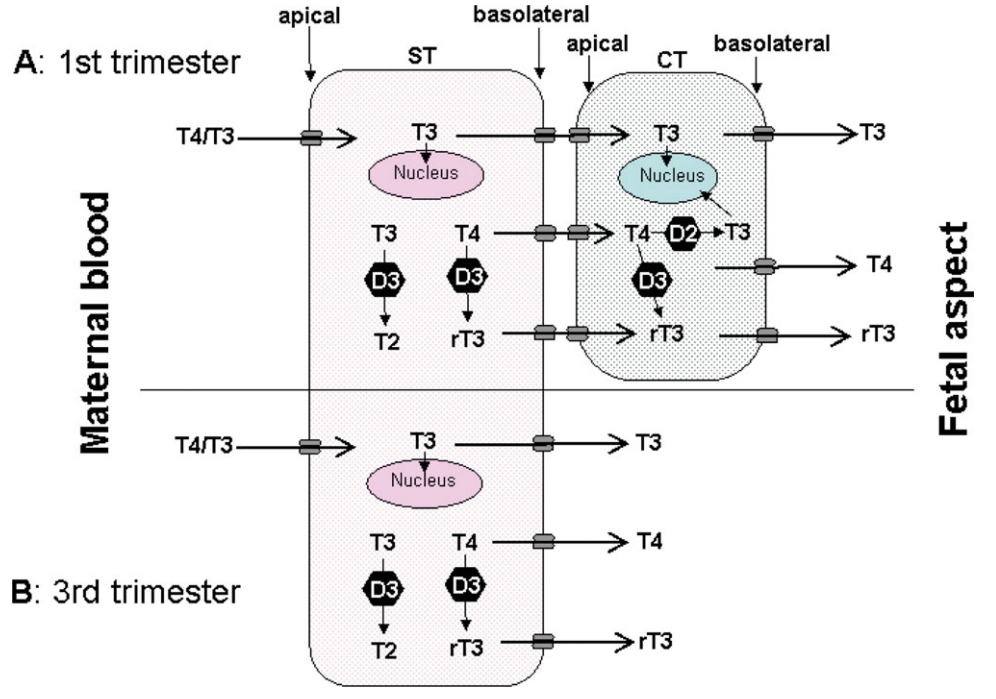

Figure 2 The passage of T4 and T3 from the maternal to fetal circulation requires negotiation through the apical membrane (maternal-facing) and the basolateral membrane (fetal-facing) of syncytiotrophoblasts (ST), and in the first half of pregnancy (A) through the plasma membranes of cytotrophoblasts (CT) as well. The localisation and function of the six different TH transporters( ) present in the placenta may differ. These include monocarboxylate transporters (MCT) 8 and 10, system-L amnio acid transporters (LAT1 and LAT2) and organic anion transporting polypeptides (OATP) 1A2 and 4A1.There may also be other yet to be identified TH transporters. In addition, T4 and T3 are subject to metabolism by deioidnase type 2 (D2) and type 3 (D3) as they pass through the trophoblasts. (Chan[9] reproduced with permission)

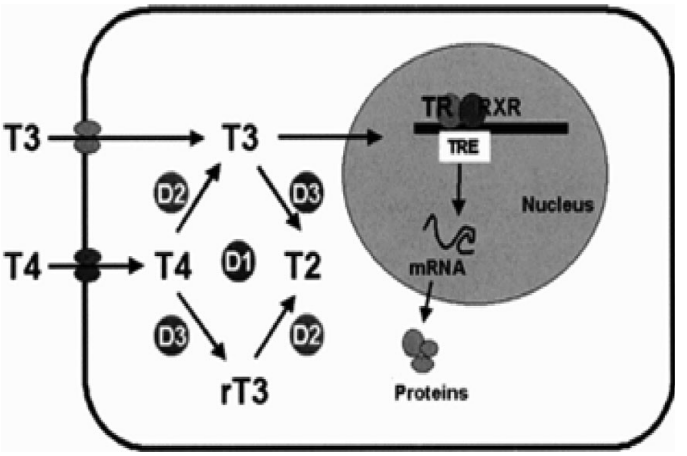

Figure 3 Thyroid hormone action and metabolism in a T3 responsive cell. The biological activity of thyroid hormone is determined by several factors. First, by the availability of the nuclear thyroid hormone receptors (TRs), which bind T3 (the active ligand) and act in conjunction with other receptors such as the retinoid X receptor (RXR) to regulate transcriptional activity. Second, by the action of deiodinase enzymes (D1, D2 and D3), which act to convert thyroid hormones between their various active and inactive forms. Third, by the expression of transporter proteins mediating the uptake (or efflux) of triidothyronine (T3) and thyroxine (T4) across the plasma membrane into the cell. (Adapted from diagram published by Jansen J[73])

in both villous and extravillous trophoblast cells. Thyroid hormone receptors are nuclear transcription factors which can bind T3 to regulate the expression of thyroid hormone responsive genes. T3 has been shown to promote proliferation, invasion and production of epidermal growth factor by 1st trimester primary trophoblast cultures.[16] In humans T3 has been shown to suppress apoptosis and down regulate Fas and Fas-ligand expression in extravillous trophoblasts.[17] It has been postulated that abnormal thyroid hormone levels could give rise to malplacentation which underlie the association between maternal thyroid dysfunction and adverse obstetric outcome.[9]

Whilst circulating thyroid hormone concentrations are major determinants of local hormone supply, their action in peripheral tissues is influenced by the activities of thyroid hormone transporters and pre-receptor regulators such as deiodinases (Figure 3). Various single-nucleotide polymorphisms associated with different levels of activity of these genes have been described between different individuals.[18] Thus, small changes in circulating thyroid hormone concentrations could potentially have significant biological impact at a tissue level, particularly within more sensitive tissues like the fetoplacental unit. Such sensitivity may be partly due to the placenta's inability to compensate for and regulate intracellular thyroid hormone concentrations through altering deiodinase activity in response to altered maternal and fetal thyroid hormone concentrations.[9]

PREGNANCY AND THYROID FUNCTION

Pregnancy affects maternal thyroid hormone production and metabolism.[19] There is an increase in thyroxine-binding globulin (TBG) concentrations due to increased hepatic synthesis and oestrogen-induced sialylation which increases the half life of TBG.[20] In addition to placental thyroid hormone metabolism by deiodinases there is increased glomerular filtration rate, renal blood flow and plasma volume leading to increased plasma iodide urinary excretion. As a result dietary iodide requirements increase to 250 micrograms per day and the WHO recommend a 250mcg supplement daily in pregnancy to ensure normal maternal thyroid hormone production is maintained. Furthermore, for women who are on thyroxine, the absorption of oral levothyroxine is reduced in pregnancy. There is also a general immunosuppressive state during pregnancy which influences autoimmune conditions such as Graves' disease.[21]

Improved sensitivity and specificity of serum TSH assays has led to a dramatic change in thyroid function testing, with TSH monitoring being the gold standard. Serum TSH levels change with gestation. In the first trimester, this TSH suppression is thought to be due to the rise in human chorionic gonadotrophin (hCG) concentrations. HCG has weak TSH activity and can stimulate the thyroid gland. TSH suppression is inversely correlated to both peak hCG and free T4 levels[22] (Figure 4). Dashe et al[23] showed in a large cohort of over 13,500 women that TSH concentrations varied according to gestation. Overall, the TSH concentration decreases in the first trimester, with its lowest level occurring around 10 weeks gestation. After this, levels rise again to reach pre-pregnancy levels in the 3rd trimester. Maternal free T4 levels peak around 10 week's gestation then decline with gestation with a significant proportion showing free T4 levels below non-pregnant values in the third trimester. In twin pregnancies, TSH suppression and free T4 rises are also more pronounced and therefore separate reference ranges should be used. By 6 weeks post partum serum TBG, TSH and maternal T4 and T3 levels return to normal.

The limitations of thyroid hormone assessment are worth emphasising. Free hormone assays, based on analogue methods that rely on the concentrations of binding-proteins, are notoriously method dependent and may give inaccurate free T3 and T4 concentrations. Direct assays with equilibrium dialysis give more accurate values, however are expensive and not widely available.[19]

Many studies have determined trimester specific TSH reference ranges.[24,25] All agree that TSH is initially suppressed in the late first trimester of pregnancy followed by a gradual rise in TSH in the second and third trimesters, however, absolute reference ranges vary. This is primarily due to studies being carried out using different assay platforms, as well as in different patient populations and therefore affected by factors such as ethnicity and iodine status.[25] Therefore reference ranges that adjust for gestation and fetal number for specific laboratory assays and specific populations would greatly improve the diagnosis of thyroid dysfunction in pregnancy.

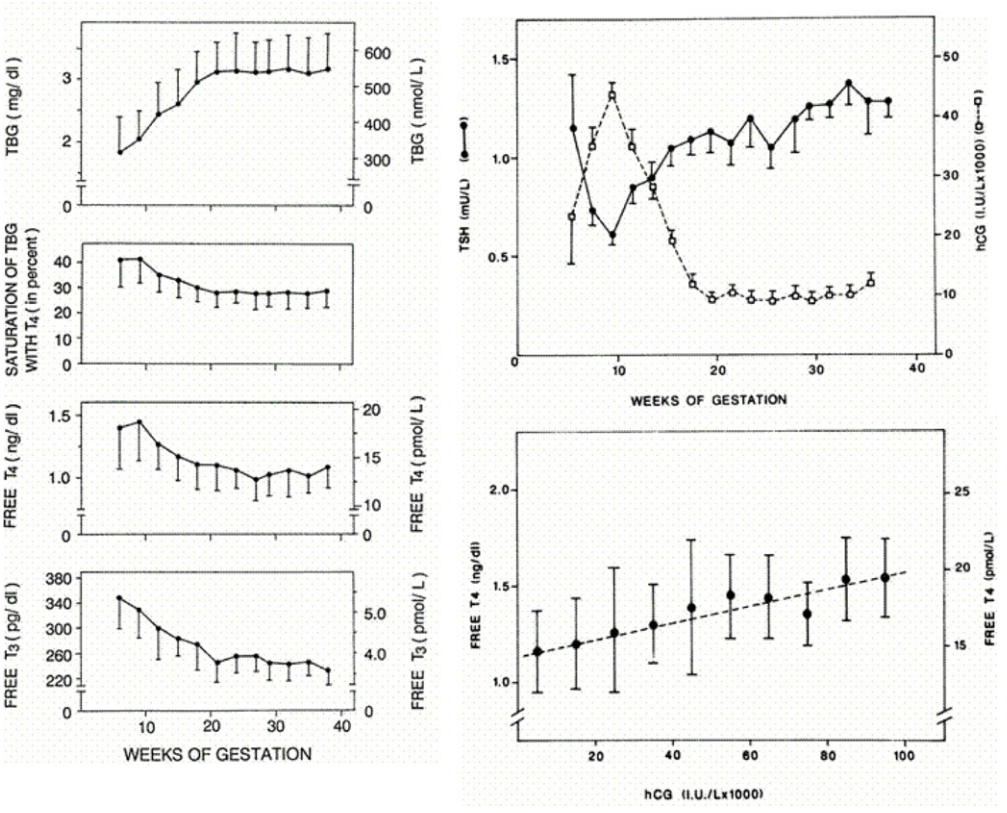

Figure 4 Gestational variation in thyroid function in normal pregnant women.
Left hand panel: Data from 606 normal pregnancies showing the rise in TBG during the first part of gestation (top) accompanied by a progressive decrease in FT4 and FT3 concentrations (bottom two) through gestation in a mildly iodine deficient area (Brussels). Right hand panel: The relationship between serum TSH and hCG as a function of gestational age (top) and the relation between FT4 and hCG in the first half of gestation (bottom). (Adapted from Glinoer[74] with permission.)

THE ROLE OF THYROID AUTOANTIBODIES

Recent studies have suggested spontaneous miscarriage occurs more commonly in women who have thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies, regardless of their thyroid function status. Similarly in animal models, TPO-induced autoimmune thyroiditis was associated with increased incidence of post-implantation fetal resorption in mice despite normal TSH and FT4.[26] Approximately 10% of women show the presence of these antibodies, but the majority are biochemically euthyroid.[27] TSH receptor antibodies are rarely present in pregnancy, however their presence indicates Graves' disease.

Two recent randomised prospective trials showed that euthyroid women with TPO antibodies who were treated with thyroxine from early pregnancy had significantly

lower rates (up to half the risk) of miscarriage and preterm delivery compared to those who were not treated.[28–30]

The mechanism of these adverse effects is not known and could involve a combination of factors:

1 Anti-TPO could directly affect fetoplacental tissues
2 Anti-TPO is associated with relative thyroid insufficiency within peripheral tissues
3 Anti-TPO is an innocent marker indicative of altered immune responses at the maternal-fetal interface
4 Anti-TPO is associated with increased maternal age which is responsible for poor obstetric outcomes.[31]

Furthermore, maternal TPO antibodies were shown to be independently associated with impaired intellectual development in offspring despite normal maternal and neonatal thyroid function.[32] The mechanisms mediating this effect also remain elusive.

The presence of thyroid autoantibodies in early pregnancy imparts a 50% risk of developing postpartum thyroid dysfunction and postpartum thyroiditis.[33]

THYROID HORMONES AND THE FETAL CENTRAL NERVOUS SYSTEM

Thyroid hormones are important for the normal development of the fetal central nervous system. The presence of ligand activated thyroid hormone receptors (TRs) early in the development of the human fetal brain supports the hypothesis that these are important for developmental events sensitive to thyroid hormones.[3] We have shown early expression of TR-alpha(α) and TR-beta (β) genes in cortical neurons and cerebellar Purkinje cells[34] as well as D2 and D3 activities in the fetal cerebral cortex from 7 weeks gestation.[35] D2 is thought to be necessary for local T3 generation from circulating T4, whilst D3 appears to protect specific brain regions from excessive T3 until the hormone is required for their development.

This notion is reinforced by the description of the spatial and temporal patterns of cerebral tissue concentrations of T3 and T4, which correlate well with the distribution of D2 and D3 activities[36] and presumed timings of thyroid hormone dependent development. The concentration of T3 is increased in the cerebral cortex between 13 and 20 weeks post menstrual age achieving levels reported in the adult and this is associated with considerable D2 but low D3 activity. However, cerebellar T3 concentration is only increased after mid gestation, coinciding with a decline in (D3) activity.

In rodent studies, thyroid deficiency may cause neurological disorders resulting from deficits in neuronal cell differentiation and migration, axonal outgrowth, myelin formation and synaptogenesis[37] but the precise mechanisms in humans are unclear.

These studies suggest that maternal thyroid hormones have an important role in mediating developmental effects early in pregnancy, which also lends support from several epidemiological studies.

Pop et al[38] have shown low maternal free T4 concentrations (lowest 10th percentile) in early gestation are associated with impaired offspring development evidenced by decreased Bayley scores when tested at 3 years. In a subgroup where spontaneous recovery of free T4 levels accrued by 32 weeks gestation, Bayley scores were no different from controls. This suggests that normalisation of maternal T4 concentrations could have a protective effect on child neurodevelopment.

Haddow et al[39] examined the IQ scores of children aged seven to nine years old born to mothers with mild asymptomatic untreated hypothyroidism in pregnancy with a TSH level above the 98th centile accompanied by borderline or a low free T4 concentration compared to control. Their scores were seven points lower than those of children born to mothers with normal TSH concentrations in pregnancy. If women were partially treated with thyroxine higher IQ score were 4 points the mean than controls, which was not statistically significant. This suggests the potential efficacy of thyroxine treatment to normalise child IQ in maternal hypothyroidism. Clinical trials have been conducted to address this issue and are discussed below.

HYPOTHYROIDISM

Incidence, prevalence and clinical aspects

In pregnant women, the prevalence of overt hypothyroidism is about 0.5–1%, with a further 2–2.5% being subclinical.[1,40,41] It is estimated that in iodine replete areas like Colorado, USA, the general population prevalence of an elevated TSH concentration is as high as 9.5%[42] and hypothyroidism is thus a common condition.

The presentation of previously undiagnosed hypothyroidism in pregnancy is not always classical and may be difficult to distinguish from the symptoms of normal pregnancy. A high index of suspicion is therefore required and clues may include the presence of risk factors such as a personal or family history of thyroid diseases and coexisting autoimmune conditions (e.g. type 1 diabetes).

OVERT HYPOTHYROIDISM

The diagnosis of overt hypothyroidism is made by observing an elevated serum TSH concentration accompanied by a low free T4 concentration. It occurs in less than 1% of pregnancies in geographical areas of iodine sufficiency but worldwide iodine deficiency is the most common cause of hypothyroidism in pregnancy. In the United Kingdom the aetiology is most commonly autoimmune thyroiditis. Other causes of hypothyroidism in pregnancy include non compliance with existing thyroxine therapy, and post-thyroid surgery, post-radioiodine treatment and hypothyroidism secondary to pituitary disease.

The effects of inadequately treated overt hypothyroidism on maternal outcomes are seen through increased incidence of miscarriage [relative risk compared to

euthyroidism (RR) 2.4], anaemia in pregnancy (31% of cases), preeclampsia (RR 3.0), placental abruption (RR 3.0) and post partum haemorrhage (19%). Poor fetal outcomes are seen through premature birth (RR 2.7), low birth weight and increased neonatal respiratory distress.[43,44] The main reason for preterm delivery and low birth weight has been attributed to gestational hypertension,[45] whilst others have associated preterm prelabour rupture of membranes accompanied by the presence of TPO antibodies, commonly present in women with hypothyroidism, as a major factor contributing to preterm delivery.[1] Hypothyroidism also leads to poor neurodevelopmental outcome in offspring.

Given the normal physiological changes described above, those women receiving thyroxine prior to conception require a dose increase from the start of pregnancy. This is extremely important to maintain normal circulating maternal thyroxine levels for supply to the placenta and the fetus, particularly in the first trimester during the critical phase of development of the central nervous system and placental unit and before the onset of fetal thyroid hormone production. Early in pregnancy, maintaining normal maternal T4 levels is crucial because the fetal thyroid gland does not produce thyroid hormones until after 16–18 weeks.[46]

Thus, women with previously diagnosed hypothyroidism on thyroxine replacement should be adequately treated. Earlier studies suggested that treatment with levothyroxine, even when inadequate, could reduce obstetric risks.[44,45] Abalovich et al[47] showed that the risk of miscarriage and preterm delivery did not depend upon whether the preconceptual diagnosis of hypothyroidism was overt or subclinical but whether adequate treatment was received. Maintaining biochemical euthyroidism during pregnancy in previously diagnosed hypothyroid women can normalize most obstetric outcomes, apart from a persistent small increased risk of pre-eclampsia (RR 1.7 compared with normal women without thyroid disease)[48] and caesarean section delivery (RR1.7).[49,50]

SUBCLINICAL HYPOTHYROIDISM AND ISOLATED HYPOTHYROXINAEMIA

Subclinical hypothyroidism and isolated hypothyroxinaemia are asymptomatic. Subclinical hypothyroidism is defined by biochemical changes showing an increased serum TSH concentration accompanied by free T4 and T3 levels within the normal range and isolated hypothyroxinaemia by normal TSH with low free T4 concentrations. Even though thyroid hormone levels are within the normal range with subclinical hypothyroidism, they may still be suboptimal for placental and nervous system development for the particular individual woman as local thyroid hormone action is also determined by other factors within peripheral tissues as discussed earlier. This may be particularly so in placental development where no local compensatory changes in deiodinase activity in response to abnormal circulating thyroid hormone levels have been described.[9] The elevated TSH concentration may give an indication of the inadequacy of the individual's tissue responses.

Subclinical hypothyroidism is also associated with adverse effects on maternal and fetal outcomes. Casey et al[40] reported a two-fold risk of delivery before 34 weeks and a three-fold risk of placental abruption amongst 404 women with subclinical hypothyroidism compared with euthyroid controls. However, there were no adverse obstetric effects found in 233 pregnant women with isolated hypothyroxinaemia.[51] In contrast, Cleary-Goldman et al[1] found no association between subclinical hypothyroidism in the first or second trimester and adverse obstetric outcomes amongst 240 women. However, they found that isolated hypothyroxinaemia (n = 232) was associated with preterm labour and birth weight greater than 4000 grams.

The issue of whether subclinical hypothyroidism newly diagnosed in pregnancy should be given thyroxine replacement remains controversial. Existing studies are all retrospective observational studies and evidence of a definite beneficial effect of thyroxine treatment in large scale prospective studies are not available. There are on-going randomised controlled trials of screening and levothyroxine treatment of subclinical thyroid dysfunction discovered in the first half of pregnancy but no data is yet available on potential obstetric impact. Nonetheless, many endocrine professional bodies[52] have advocated levothyroxine treatment of subclinical hypothyroidism given the highly favourable potential benefit to risk ratio of therapy. By contrast the ACOG[53,54] have not endorsed recommendations to universally screen for maternal subclinical thyroid dysfunction nor do they agree with treatment of subclinical hypothyroidism in pregnancy. Neither endocrine nor obstetric professional bodies have issued any recommendations yet about whether isolated hypothyroxinaemia should be treated in pregnancy.

CASE FINDING VS. UNIVERSAL SCREENING FOR MATERNAL THYROID DYSFUNCTION

A prospective study by Negro *et al*[55] set out to determine whether universal screening versus a strategy of case finding for detection and treatment of thyroid dysfunction made any difference to overall incidences of adverse obstetric outcomes. Case finding involves only screening women at high risk of thyroid dysfunction which include a known personal or family history of thyroid disease, goitre, symptoms or signs of thyroid dysfunction, type 1 diabetes, other autoimmune disorders, infertility and history of recurrent miscarriage or head/neck irradiation. The group of women randomised to universal screening did not demonstrate an overall decreased rate of adverse obstetric outcome compared to those randomised to case finding since the majority of adverse events occurred in the euthyroid population. In a sub-analysis, however, women at low risk of thyroid dysfunction who where found through universal screening to have occult hyperthyroidism (and thus treated with anti-thyroidals) or to be subclinically hypothyroid with anti-TPO (and thus treated with levothyroxine), did experience fewer adverse outcomes compared to the low risk women in the case finding group who were retrospectively found to have thyroid dysfunction and thus not treated antenatally.

The number needed to treat was 1.8 to prevent an adverse outcome in this group. However, the substudy was inadequately powered to show a statistically significant difference. Overall, due to the low frequency of thyroid function abnormalities, 36 women must be screened to identify 1 woman requiring treatment and 60 women would need to be screened to prevent one adverse outcome. Nonetheless, this study suggests that the detection of subclinical thyroid disease in the first trimester and its treatment could potentially reduce the risks of adverse obstetric outcomes. Larger studies are required to confirm this.

Two other studies showed that a strategy of case finding failed to identify the majority of women with thyroid function abnormalities.[56,57] Screening those with risk factors only detected 30% of hypothyroid and 69% of hyperthyroid women.[56] The American Association of Clinical Endocrinologists in 2002 recommended screening all women considering conception and pregnant women for thyroid dysfunction.[58] However, due to the absence of evidence of treatment benefit from completed interventional studies, in 2007 The Endocrine Society Clinical Practice Guideline on the management of thyroid dysfunction during pregnancy recommended only case finding among high risk pregnant women.[52]

Information on effects of screening and treatment in relation to neurodevelopment are sparse. It is clear that correction of iodine deficiency during pregnancy prevents adverse fetal neural development.[59]

Preliminary analysis of the neurodevelopmental outcomes of the recently completed Wales CATS study, a prospective randomised control trial of screening and levothyroxine treatment of maternal subclinical hypothyroidism and isolated hypothyroxinaemia before 16 weeks gestation have shown no beneficial effect upon offspring mean IQ score at age 3.[60] A secondary analyses which excluded cases where there was no significant change in the thyroid function 6 weeks following commencement of levothyroxine treatment did find that the proportion of children with an IQ less than 85 was significantly lower in the screened than control group (OR 0.6). Importantly, assessment of maternal thyroid function in this study, and initiation of levothyroxine when indicated, occurred at 12 weeks of gestation or thereafter. The result of the secondary analyses hint at the possibility that levothyroxine could still be effective if started earlier. In the CATS study there were no differences in mean gestational age at delivery and in birth weight but detailed analyses of obstetric outcomes is still to be completed. The potential benefits of treatment are clear and the potential risks of treatment are negligible and these should be discussed with patients to decide if levothyroxine treatment should be given in subclinical thyroid dysfunction.

CORRELATIONS BETWEEN OBSTETRIC OUTCOMES AND THYROID FUNCTION ACROSS THE REFERENCE RANGE

Even when both TSH and free T4 concentrations have been within the normal reference ranges (2.5th to 97.5th percentile) or at the limits of normality, increased

risk of adverse outcomes have been reported for higher TSH and lower free T4 concentrations.

Interestingly a study in the Netherlands reported an increased incidence of breech presentation (11%) associated with women with TSH concentrations above the 90th percentile at 36 weeks gestation[61] compared with 4.8% in women with TSH below this cut-off. Wijnen et al[62] found nonoccipital-anterior fetal head position in labour was associated with lower free T4 concentrations (OR 0.88 for every pmol/L increase in free T4) and a similar relationship was found between instrumental deliveries for occipital-anterior positions and lower free T4 levels (OR 0.91 for every pmol/L increase in free T4).

It has also been reported that thyroid function may also be associated with the development of late preeclampsia where TSH concentrations were elevated and free T4 concentrations were decreased.[63]

Benhadi et al[64] found an increased incidence of miscarriage and perinatal loss by a factor of 60% for every doubling of the TSH concentration (OR 1.8 after adjustment of confounding factors). These findings have also been demonstrated by Ashoor et al[65] who found higher prevalences of raised maternal serum TSH concentration and low free T4 concentrations amongst pregnancies ending in miscarriage or fetal death in the second or third trimesters compared with pregnancies of normal outcome. Negro et al[66] also found that TSH levels between 2.5 and 5.0 mU/L (at the upper end or just above the normal range) in the first trimester in TPO antibody negative women were associated with a significant increase in miscarriage.

CLINICAL MANAGEMENT OF HYPOTHYROIDISM IN PREGNANCY

Levothyroxine is the treatment of choice. Approximately 80% of ingested levothyroxine is absorbed from the gastrointestinal tract with even less during pregnancy. Serum T4 levels peak two to four hours after levothyroxine ingestion and remain so for up to six hours. T3 levels rise at a much slower rate due to the conversion of T4 to T3.

The British Thyroid Association guidelines recommend that women on thyroxine treatment should aim to keep the TSH in the lower part of the normal range (below 2.0 mU/L) and free T4 in the upper part of the normal range.[67] The normal range is classically defined as those values between 2.5–97.5 percentile for the specified population. This recommendation is fitting since adverse effects have been described at the upper end of the TSH reference range and the lower end of the free T4 range. Provided the woman is clinically euthyroid, TSH can be considered normal even when as low as 0.1 mU/L since subclinical hyperthyroidism (low TSH with normal free T4) was not associated with adverse outcomes.[68] Equally, with TSH levels within the normal range, a slightly high free T4 result does not require a change in dosage since TSH is the more

sensitive marker of thyroid insufficiency during pregnancy in the context of iodine sufficiency and free T4 estimations are more inaccurate in pregnancy as described above.

In the Clinical Practice guideline,[52] the recommended TSH for the first trimester is below 2.5 mU/L, and in the 2nd and 3rd trimester below 3.0mU/L, in the absence of locally defined gestation specific reference ranges.

Most studies support increasing levothyroxine doses at the start of pregnancy to maintain a euthyroid state with further monitoring of TSH and T4 concentrations to ensure correct replacement doses with advancing gestation.[69,70] One study found that on average a 47% increase in thyroxine requirements occurred during the first half of pregnancy in 85% of hypothyroid women. The need for increase occurred as early as 5 weeks gestation with a median onset of increase of 8 weeks gestation.[69] The most recent study found that 87% of women required a dose increase one or more times during the course of pregnancy.[71]

The Thyroid Hormone Early Adjustment in Pregnancy (THERAPY) Trial[72] investigated how best to achieve biochemical euthyroidism throughout pregnancy to minimize the risks of hypo- and hyperthyroidism in women with pre-existing hypothyroidism treated with levothyroxine. The data demonstrated that doubling the levothyroxine dose on 2 days each week upon confirmation of pregnancy could prevent the development of maternal hypothyroidism during pregnancy in 85% of cases and mimics normal physiology. The authors recommend preconception advice to those patients with known thyroid dysfunction. Thyroid function testing every 4 weeks until 20 weeks gestation would detect 92% of abnormal TSH values which would trigger further dose adjustments. The thyroid function should be checked again at least once at the start of the 3rd trimester.

Ideally thyroid function should be normalised prior to conception and family doctors play a key role in providing preconception advice. Despite the median study enrolment in Yassa et al's study[72] being 5.5 weeks gestation, 30% of women who had a normal TSH pre-conception were already hypothyroid with elevated TSH levels when first seen in pregnancy. Therefore empirical dose increase is recommended to prevent hypothyroidism. As most women do not present themselves to antenatal clinics until at least 8–12 weeks gestation, the importance of patient's understanding of increasing their own levothyroxine doses early in gestation should be emphasised. Following initial dose increases, a further dose adjustment was required in over 40% of women in the THERAPY study, underlining the importance of monitoring in pregnancy.

Yassa et al[72] found three factors that helped identify those patients at greatest risk of over replacement with thyroxine that require closer monitoring or more conservative adjustment of levothyroxine. Patients without a thyroid gland secondary to surgery or ablation, patients with prepregnancy TSH concentrations under 1.5 mlU/liter and those receiving prepregnancy levothyroxine doses of at least 100 micrograms. They have an up to 7 fold increased risk of TSH suppression after the initial levothyroxine increase, but a transient TSH suppression is not thought to be harmful.

CONCLUSION

Hypothyroidism in pregnancy is associated with adverse fetal and maternal outcomes. Early treatment of overt hypothyroidism may minimise these risks. Preconception planning is vital in achieving best outcomes.

The placenta regulates the amount of thyroid hormones, primarily T4, available from the mother to the fetus. Placental tissue is responsive to thyroid hormone, and abnormal thyroid hormone levels could give rise to malplacentation which may mediate the association between maternal thyroid dysfunction and adverse obstetric outcomes.

Recent studies have suggested spontaneous miscarriage and preterm labour occur more frequently in those women with TPO antibodies. The mechanism of these adverse effects is currently unclear and further investigation is required to determine whether these antibodies directly affect the fetoplacental unit or are a marker of thyroid insufficiency.

Maintaining euthyroidism throughout gestation remains the cornerstone of hypothyroid management. This can be achieved through adequate preconception thyroxine replacement, empirical increase in thyroxine doses at confirmation of conception and regular thyroid function monitoring in pregnancy using gestation specific reference ranges.

Universal screening for subclinical hypothyroidism still remains controversial. There is already a move towards targeted screening of pregnant women with risk factors for thyroid disease, but studies have demonstrated that such a strategy may exclude 30–50% of women with thyroid dysfunction. The demonstration of definite benefits of universal screening and levothyroxine intervention on obstetric and neurodevelopmental outcomes in large interventional studies are still lacking. We have to await the results of on-going prospective studies of screening and treatment of subclinical thyroid dysfunction and thyroid autoimmunity to draw further conclusions regarding the potential obstetric and offspring benefits of such a programme.

REFERENCES

1 Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008; **112**: 85–92.

2 Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001; **81**: 1097–142.

3 de Escobar GM, Ares S, Berbel P, Obregon MJ, del Rey FE. The changing role of maternal thyroid hormone in fetal brain development. *Semin Perinatol* 2008; **32**: 380–86.

4 Calvo RM, Jauniaux E, Gulbis B, Asuncion M, Gervy C, Contempre B et al. Fetal tissues are exposed to biologically relevant free thyroxine concentrations during early phases of development. *J Clin Endocrinol Metab* 2002; **87**: 1768–777.

5 Contempre B, Jauniaux E, Calvo R, Jurkovic D, Campbell S, de Escobar GM. Detection of thyroid hormones in human embryonic cavities during the first trimester of pregnancy. *J Clin Endocrinol Metab* 1993; **77**: 1719–722.

6 Sinha AK, Prabakaran D., Godbole M, Chattopadhyay N, Karmarkar M, Pickard MR et al. Hendrich CE (ed.) Thyroid hormone and brain maturation. *Recent research developments in neuroendocrinology* Trivandrum: India, Research Signpost 1997; 1–14.

7 Vulsma T, Gons MH, de Vijlder JJ. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med* 1989; **321**: 13–16.

8 Delahunty C, Falconer S, Hume R, Jackson L, Midgley P, Mirfield M et al. Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5 1/2 years: millennium cohort study. *J Clin Endocrinol Metab* 2010; **95**: 4898–908.

9 Chan SY, Vasilopoulou E, Kilby MD. The role of the placenta in thyroid hormone delivery to the fetus. *Nat Clin Pract Endocrinol Metab* 2009; **5**: 45–54.

10 Hume R, Simpson J, Delahunty C, van Toor H, Wu SY, Williams FLR et al. Human fetal and cord serum thyroid hormones: Developmental trends and interrelationships. *J Clin Endocrinol Metab* 2004; **89**: 4097–103.

11 Richard K, Hume R, Kaptein E, Stanley EL, Visser TJ, Coughtrie MW. Sulfation of thyroid hormone and dopamine during human development: ontogeny of phenol sulfotransferases and arylsulfatase in liver, lung, and brain. *J Clin Endocrinol Metab* 2001; **86**: 2734–742.

12 Farwell AP, Dubord-Tomasetti SA, Pietrzykowski AZ, Leonard JL. Dynamic nongenomic actions of thyroid hormone in the developing rat brain. *Endocrinology* 2006; **147**: 2567–574.

13 Mortimer RH, Galligan JP, Cannell GR, Addison RS, Roberts MS. Maternal to fetal thyroxine transmission in the human term placenta is limited by inner ring deiodination. *J Clin Endocrinol Metab* 1996; **81**: 2247–249.

14 Chan S, Kachilele S, Hobbs E, Bulmer JN, Boelaert K, McCabe CJ et al. Placental iodothyronine deiodinase expression in normal and growth-restricted human pregnancies. *J Clin Endocrinol Metab* 2003; **88**: 4488–495.

15 Loubiere LS, Vasilopoulou E, Bulmer JN, Taylor PM, Stieger B, Verrey F et al. Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction. *Placenta* 2010; **31**: 295–304.

16 Maruo T, Matsuo H, Mochizuki M. Thyroid hormone as a biological amplifier of differentiated trophoblast function in early pregnancy. *Acta Endocrinol (Copenh)* 1991; **125**: 58–66.

17 Laoag-Fernandez JB, Matsuo H, Murakoshi H, Hamada AL, Tsang BK, Maruo T. 3,5,3′-triiodothyronine down-regulates Fas and Fas ligand expression and suppresses caspase-3 and poly (adenosine 5′-diphosphate-ribose) polymerase cleavage and apoptosis in early placental extravillous trophoblasts in vitro. *J Clin Endocrinol Metab* 2004; **89**: 4069–4077.

18 van der Deure WM, Peeters RP, Visser TJ. Genetic variation in thyroid hormone transporters. *Best Pract Res Clin Endocrinol Metab* 2007; **21**: 339–50.

19 Lazarus JH. Thyroid function in pregnancy. *Br Med Bull* 2011; **97**: 137–48.

20 Fantz CR, gogo-Jack S, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. *Clin Chem* 1999; **45**: 2250–258.

21 Hegde UC. Immunomodulation of the mother during pregnancy. *Med Hypotheses* 1991; **35**: 159–64.

22 Glinoer D, De NP, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest* 1993; **16**: 881–88.

23 Dashe JS, Casey BM, Wells CE, McIntire DD, Byrd EW, Leveno KJ et al. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. *Obstet Gynecol* 2005; **106**: 753–57.

24 Soldin OP. Thyroid function testing in pregnancy and thyroid disease: trimester-specific reference intervals. *Ther Drug Monit* 2006; **28**: 8–11.

25 Glinoer D, Spencer CA. Serum TSH determinations in pregnancy: how, when and why? *Nat Rev Endocrinol* 2010; **6**: 526–29.

26 Lee YL, Ng HP, Lau KS, Liu WM, WS O, Yeung WS et al. Increased fetal abortion rate in autoimmune thyroid disease is related to circulating TPO autoantibodies in an autoimmune thyroiditis animal model. *Fertil Steril* 2009; **91**(5 Suppl): 2104–109.

27 Stagnaro-Green A, Glinoer D. Thyroid autoimmunity and the risk of miscarriage. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 167–81.

28 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**: 1529–533.

29 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**: 2587–591.

30 Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn JA, Coomarasamy A. Thyroid auto-antibodies are strongly associated with miscarriage and preterm birth: A meta-analysis of evidence. *BMJ*, In press. 2011.

31 Kaprara A, Krassas GE. Thyroid autoimmunity and miscarriage. *Hormones (Athens)* 2008; **7**: 294–302.

32 Pop VJ, de Vries E, van Baar AL, Waelkens JJ, de Rooy HA, Horsten M et al. Maternal thyroid peroxidase antibodies during pregnancy: a marker of impaired child development? *J Clin Endocrinol Metab* 1995; **80**: 3561–566.

33 Stagnaro-Green A. Recognizing, understanding, and treating postpartum thyroiditis. *Endocrinol Metab Clin North Am* 2000; **29**: 417–30, ix.

34 Kilby MD, Gittoes N, McCabe C, Verhaeg J, Franklyn JA. Expression of thyroid receptor isoforms in the human fetal central nervous system and the effects of intrauterine growth restriction. *Clin Endocrinol (Oxf)* 2000; **53**: 469–77.

35 Chan S, Kachilele S, McCabe C, Tannahill L, Boelaert K, Gittoes N et al. Early expression of thyroid hormone deiodinases and receptors in human fetal cerebral cortex. *Brain Res Dev Brain Res* 2002; **138**: 109–16.

36 Kester MHA, de Mena RM, Obregon MJ, Marinkovic D, Howatson A, Visser TJ et al. Iodothyronine levels in the human developing brain: Major regulatory roles of iodothyronine deiodinases in different areas. *J Clin Endocrinol Metab* 2004; **89**: 3117–128.

37 Bernal J. Thyroid hormone receptors in brain development and function. *Nat Clin Pract Endocrinol Metab* 2007; **3**: 249–59.

38 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**: 282–88.

39 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. *N Engl J Med* 1999; **341**: 549–55.

40 Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005; **105**: 239–45.

41 Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A et al. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991; **35**: 41–46.

42 Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; **160**: 526–34.

43 LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? *Thyroid* 2005; **15**: 60–71.

44 Davis LE, Leveno KJ, Cunningham FG. Hypothyroidism complicating pregnancy. *Obstet Gynecol* 1988; **72**: 108–12.

45 Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. *Obstet Gynecol* 1993; **81**: 349–53.

46 de Escobar GM, Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 225–48.

47 Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002; **12**: 63–68.

48 Wolfberg AJ, Lee-Parritz A, Peller AJ, Lieberman ES. Obstetric and neonatal outcomes associated with maternal hypothyroid disease. *J Matern Fetal Neonatal Med* 2005; **17**: 35–38.

49 Matalon S, Sheiner E, Levy A, Mazor M, Wiznitzer A. Relationship of treated maternal hypothyroidism and perinatal outcome. *J Reprod Med* 2006; **51**: 59–63.

50 Idris I, Srinivasan R, Simm A, Page RC. Maternal hypothyroidism in early and late gestation: effects on neonatal and obstetric outcome. *Clin Endocrinol (Oxf)* 2005; **63**: 560–65.

51 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. *Obstet Gynecol* 2007; **109**: 1129–135.

52 Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D et al. Management of thyroid dysfunction during pregnancy and postpartum: An endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2007; **92**: S1–S7.

53 ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy. *Obstet Gynecol* 2007; **110**: 959–60.

54 ACOG practice bulletin. Thyroid disease in pregnancy. Number 37, August 2002. American College of Obstetrics and Gynecology. *Int J Gynaecol Obstet* 2002; **79**: 171–80.

55 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**: 1699–707.

56 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**: 203–207.

57 Wang W, Teng W, Shan Z, Wang S, Li J, Zhu L et al. The prevalence of thyroid disorders during early pregnancy in China: the benefits of universal screening in the first trimester of pregnancy. *Eur J Endocrinol* 2011; **164**: 263–68.

58 Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract* 2002; **8**: 457–69.

59 Pharoah PO, Connolly KJ. Iodine and brain development. *Dev Med Child Neurol* 1995; **37**: 744–48.

60 Lazarus JH. Outcome of the CATS Study in Pregnant Women. 15-9-2010. 14th International Thyroid Congress, Paris. Ref Type Unpublished

61 Kuppens SM, Kooistra L, Wijnen HA, Crawford S, Vader HL, Hasaart TH et al. Maternal thyroid function during gestation is related to breech presentation at term. *Clin Endocrinol (Oxf)* 2010; **72**: 820–24.

62 Wijnen HA, Kooistra L, Vader HL, Essed GG, Mol BW, Pop VJ. Maternal thyroid hormone concentration during late gestation is associated with foetal position at birth. *Clin Endocrinol (Oxf)* 2009; **71**: 746–51.

63 Ashoor G, Maiz N, Rotas M, Kametas NA, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent development of preeclampsia. *Prenat Diagn* 2010; **30**: 1032–1038.

64 Benhadi N, Wiersinga WM, Reitsma JB, Vrijkotte TG, Bonsel GJ. Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *Eur J Endocrinol* 2009; **160**: 985–91.

65 Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. *Thyroid* 2010; **20**: 989–93.

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

67 Association of Clinical Biochemists (ACB), British Thyroid Association (BTA), British Thyroid Foundation (BTF). UK guidelines for the use of thyroid function tests (http://www.acb.org.uk/docs/TFTguidelinefinal.pdf). 2006; 39–43.

68 Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. *Obstet Gynecol* 2006; **107**: 337–41.

69 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. *New Eng J Med* 2004; **351**: 241–49.

70 Mandel SJ. Hypothyroidism and chronic autoimmune thyroiditis in the pregnant state: maternal aspects. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 213–24.

71 Verga U, Bergamaschi S, Cortelazzi D, Ronzoni S, Marconi AM, Beck-Peccoz P. Adjustment of L-T4 substitutive therapy in pregnant women with subclinical, overt or post-ablative hypothyroidism. *Clin Endocrinol (Oxf)* 2009; **70**: 798–802.

72 Yassa L, Marqusee E, Fawcett R, Alexander EK. Thyroid Hormone Early Adjustment in Pregnancy (The THERAPY) Trial. *J Clin Endocrinol Metab* 2010; **95**: 3234–241.

73 Jansen J, Friesema EC, Milici C, Visser TJ. Thyroid hormone transporters in health and disease. *Thyroid* 2005; **15**: 757–68.

74 Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997; **18**: 404–33.