Management of subclinical hypothyroidism in pregnancy: are we too simplistic?

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Abstract

Guideline advice of many societies on the management of subclinical hypothyroidism in pregnancy suggests treatment when TSH serum levels exceed 2.5 mU/l. Justification of this procedure is based on limited experience, mainly from studies carried out in patients with positive thyroid-specific antibodies and higher TSH levels that classically define the condition in the non-pregnant state. Taking into account a lack of clear understanding of the regulation of thyroid hormone transport through the utero-placental unit and in the absence of foetal markers to monitor the adequacy of thyroxine treatment, this review attempts to discuss currently available data and suggests a more cautious approach.

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Current guideline aims and epidemiology

Management of overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) in pregnancy has been systematically reviewed in the guidelines of several societies: The American Endocrine Society (TES), the American Thyroid Association (ATA) jointly with the American Association of Clinical Endocrinologists (AACE) and most recently by the European Thyroid Association (ETA) (1, 2, 3, 4). OH diagnosed during pregnancy requires immediate treatment with thyroid hormones (THs), which is undisputed in order to avoid the potentially devastating effects of hypothyroidism on cognitive function of the offspring and to reduce pregnancy-associated risks to the foetus and the mother (5). In all these guidelines, there is also consensus that SCH – defined as serum thyroid-stimulating hormone (TSH) concentrations above 2.5 mU/l (preconception and in the first trimester) with normal

circulating TH levels – should be treated with levothyroxine (L-T₄) replacement. In addition, isolated hypothyroxinaemia (normal TSH and reduced free thyroxine (fT₄) concentrations) is regarded as a different entity, which will not be further discussed in depth in this manuscript.

The TES guideline targets both SCH patients who are TPO-Ab negative and those who are TPO-Ab positive (1.2.2 TES guideline), rating the evidence to treat as poor to fair but states that 'potential benefits outweigh the potential risks' (2). ATA/AACE guidelines also suggests treatment of all SCH pregnant women regardless of the antibody status when TSH serum concentrations exceed the pregnancy-specific upper limits of 2.5 mU/l in the first trimester and 3.0 or 3.5 mU/l in the following trimesters respectively (1). All guidelines agree that 'it is reasonable practice to maintain TSH values in women planning pregnancy below 2.5 mU/l, especially in those with positive TPO-Ab;

newly diagnosed patients should be treated in order to normalise maternal serum TSH values within the trimester-specific pregnancy reference range (3)'. The recent ETA guideline, which generally agreed on a TSH threshold of >2.5 mU/l for starting T_4 substitution, has discussed this question even more controversially by stating that 'the debate about substitution therapy in SCH is still open both for non-pregnant and pregnant patients', but remained in favour of treatment because the panel believed that ' T_4 treatment of SCH would appear to have the potential benefits which outweigh the potential risks' (3).

Since the first publication of a specific guideline on the management of thyroid dysfunction in pregnancy by TES in 2007 (6), major changes in clinical practice have been observed in many countries. Screening, generally discussed as an open question (3), is now a reality in many countries and close surveillance of TSH with an upper threshold of 2.5 mU/l now drives treatment primarily by gynaecologists and centres for reproductive medicine. A clear benefit of screening has been an increase in the detection rate of thyroid dysfunction which helps to improve the well-recognised problem of undetected OH (7). The rate of OH varied between 0.25 and 0.91% in large population studies carried out in a total of 104 557 participants (7, 8, 9), whereas screening has also resulted in the diagnosis of SCH in 3–10% of pregnancies, depending on the TSH cut-off and assay platform used (9, 10). A recent Chinese study (11) has reported that up to 30% of pregnant women in early pregnancy were classed as having SCH if the generic cut-off of 2.5 mU/l was used. Not all of them will have thyroid disease, as a recent investigation in completely healthy non-pregnant young women from Denmark suggests that 10–15% spontaneously have TSH levels >2.5 mU/l (12). Furthermore, a study carried out in healthy, pregnant, iodine sufficient (13) women from The Netherlands showed that $>10\%$ of TPO-Ab-negative women had a TSH level above 2.5 mU/l in the first trimester.

Here we would like to discuss the pathophysiological basis of interventions in SCH and the currently available markers for monitoring mother and offspring during the management of SCH to add some caution to the current approach.

Changes of TSH, THs and iodine during pregnancy

Normal pregnancy has profound impacts on thyroid function. Placental production of human chorionic

gonadotrophin (hCG) and a rise in oestrogen production that increases binding proteins, namely thyroxine-binding globulin affect free TH levels. TSH dips according to most but not all studies within the first trimester, whereas free TH concentrations decrease, albeit very slightly, mainly during the latter part of pregnancy (10, 11, 14, 15, 16, 17, 18, 19). These observed alterations are not only due to pathophysiological changes but are, at least in part, due to methodological issues.

Placental production of hCG alters circulating TSH concentrations because hCG at high concentrations acts as an activator of the TSH receptor (14, 15). hCG's rapid increase in the first trimester of pregnancy is therefore viewed as being essential for a higher synthesis and release of T_4 from the thyroid. Another crucial factor that can alter TSH levels in pregnancy is iodine availability. From early pregnancy, renal clearance of iodine is reported to increase (20), in parallel with the increase in glomerular filtration rate (21). This may profoundly impact on the sensitivity or responsiveness of the thyroid to TSH and hence TH release. Experimental evidence suggests that, in humans, TSH decreases but thyroglobulin increases in mild iodine deficiency (22). Detailed animal studies as well as data obtained for humans on the uptake of radioactive iodine indicate that in nutritional iodine deficiency there is an increased sensitivity of the thyroid to TSH, resulting in most of the follicles being actively involved in thyroid function. This is in contrast to the thyroid exposed to normal dietary iodine supply, where only scattered, solitary follicles are active (23, 24, 25). A recent large epidemiological study carried out in children and adolescents supports this notion of the fine tuning of thyroidal TSH-responsiveness by iodine as TSH concentrations were decreased with circulating TH concentrations maintained in iodine deficiency (26).

In pregnancy, a similar delicate adaptation of the maternal thyroid function may take place. Comparable to the above mentioned studies, a decrease in iodine availability – as anticipated by the increased renal clearance of iodine in pregnancy – may contribute to the decrease in maternal TSH levels in early pregnancy. This would explain some epidemiological data supporting a positive correlation between TSH level and urinary iodine concentration (16, 27, 28), but is contradicted in a large cross-sectional Chinese study conducted for measuring TSH and iodine excretion within the first trimester of pregnancy, showing that serum TSH concentrations did not differ in non-pregnant women during the first 6 weeks of pregnancy, but only between weeks 7 and 12 of pregnancy a significant decrease was found (11).

Interestingly, these changes were independent from urinary iodine excretion, which indicated adequate iodine supply and were comparable between pregnant and non-pregnant women.

The depth, rate and timing of the first-trimester dip in TSH scatter widely between studies and with marked interindividual variability within studies (10, 14, 15, 17, 18, 19). Methodological differences amongst TSH assay platforms may explain some of the variation. A recently published comparison of seven different frequently used assay systems for TSH and fT_4 in samples obtained in the first trimester of pregnancy revealed a more than 40% variation between assay results of the same sera suggesting that a firm cut-off of 2.5 mU/l in one assay may correspond to a higher level with another, sometimes by as much as 1 mU/l or more (29). The calculation of assay-specific multiples of the median (MoM) values may overcome these limitations as recently proposed, and may better homogenise the assay variations (30). This, however, relies on the availability of assay-specific normative data, frequently demanded but very rarely instituted in every day practice.

In addition to assay variations, other population characteristics such as iodine intake, ethnicity and BMI likely contribute to these substantial differences in TSH between different populations. A recent multi-ethnic population-based pregnancy cohort from European origin has shown substantial differences in the upper limits of TSH (as determined by the 97.5th percentile in TPO-Ab negative women) between different ethnic groups. For example the upper limit of TSH was 4.18 mU/l in women from Dutch origin compared with 3.58 mU/l in women living in the same region but from Moroccan origin (31). In a Scandinavian study, women with a BMI <20 kg/m² showed that the upper limit (P95) for TSH increased from 2.86 to 3.50 mU/l compared with women with a BMI >30 kg/m² (32).

The magnitude of decrease of free TH levels during the course of pregnancy is subject to high variability as well (33). This may in part be explained by a variable impact of pregnancy-associated changes in binding proteins on the different assay systems as tested by Feldt-Rasmussen *et al.* (34). When calculating MoM, this variability is much lower with a consistent decrease in fT_4 from the first to third trimesters of pregnancy by ~20%, with extremes of 10 and 30% respectively. Only the measurement of fT_4 with tandem mass-spectrometry, currently regarded as the gold standard, shows a much greater decrease in fT_4 by ~50% (35).

The mechanisms behind these changes and their relevance to the control of foetal TH homeostasis have not been fully elucidated. They may be driven by a lower availability of free TH in the maternal circulation due to

the altered binding protein expression and an increased TH metabolism driven by the placental expression of deiodinase type 3 (D3), as well as by an increasing transfer of THs to the foetus with advancing gestation.

Evidence for adverse effects of SCH during pregnancy

Careful assessment of the existing literature in the framework of all guidelines left no doubt that untreated or inadequately treated OH leads to an array of pregnancy complications, namely preeclampsia, gestational hypertension, cretinism, foetal death and spontaneous miscarriage (36). Despite those, several reports of severe OH did not show an increased rate of pregnancy-related complications, suggesting that even severe hypothyroidism does not necessarily preclude normal pregnancy outcomes nor induce complications (37).

What is the evidence for adverse effects of SCH in pregnancy? Based on the cited literature in the guidelines, a range of effects is described, but the number of affected cases in most studies is small and data are not consistent when focusing on various aspects of pregnancy complications. It is beyond the scope of this paper to discuss all studies investigating these different pregnancy complications in detail. For this reason, we will predominantly focus on miscarriage rate as one of the best-studied pregnancy complications. The diversity in results is highlighted in two studies on the miscarriage rate in SCH. One was a prospective investigation of the rate of pregnancy loss in TPO-negative women with TH concentrations within the classically defined non-pregnant normal range (38). The percentage of miscarriage was almost doubled when TSH in the first trimester of pregnancy was between 2.5 and 5 mU/l as compared with a TSH <2.5 mU/l. In absolute numbers, it was based on 39 pregnancy losses of 642 pregnancies (6.1%) in the TSH of range 2.5–5.0 mU/l group as compared with 127/3481 (3.6%) in pregnancies with TSH below 2.5 mU/l. However, in another larger prospective study of 240 patients with SCH and TSH concentrations >4.29 mU/l with normal TH concentrations, there was no difference in miscarriage rate as compared with almost 10 000 healthy controls. Eighty-five percent of these patients were TPO-Ab negative and there was no difference in any other pregnancy-associated complications (39). The problems of comparisons between studies are highlighted in a recent meta-analysis showing a wide scatter in the definitions of SCH, the population characteristics including iodine status as well as the timing of recruitment and testing across 16 studies with a total of

Position Statement	G Brabant and others	Critical review of subclinical hypothyroidism in pregnancy	173:1	P4
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2573 cases of SCH in 49 545 pregnancies (9). Not all studies reported an increased miscarriage rate.

What are potential alternative explanations for the reported differences in pregnancy outcomes? One possibility is the associated immune dysfunction commonly seen in autoimmune conditions. The rate of miscarriage is believed to be higher in patients with a positive history of autoimmune disease, not just of thyroid origin but also in diagnoses such as systemic lupus erythematosus (SLE) and type 1 diabetes. In a recent meta-analysis by Thangaratnam *et al.* (40), the rate of pregnancy complications has been linked to thyroid autoimmunity showing significantly higher rates of complications in antibody positive women than in antibody negative controls, despite biochemical euthyroidism. Interaction of TSH receptor autoantibodies with receptors for gonadotrophins may represent one mechanism to explain the increased prevalence of problems in pregnancies of mothers with autoimmune thyroid disease, but a number of other mechanisms including associated immune dysregulation targeting particularly the reproductive tract and/or the foeto-placental unit have been discussed (41, 42). This is confirmed by a recent larger prospective study that has shown a stepwise increase in miscarriage rates with thyroid autoimmunity alone and in combination with SCH (43).

Despite these findings, the frequency of miscarriage reported in smaller studies is difficult to judge against expectations from large population-based investigations because data on the frequency of miscarriage in the first weeks of pregnancy vary considerably. More than 70% of pregnancies may spontaneously miscarry within the first 6 weeks (a significant proportion unnoticed) and the prevalence thereafter is given as ~10%, depending on factors including the time from conception, age or ethnicity (44). Hence many existing studies have underestimated miscarriage rates as a recruitment that typically begins after 6 weeks gestation. Hopefully this problem, which is common to all existing studies, will be substantially improved by the ongoing TABLET and T4LIFE RCTs which recruit and randomise TPO-Ab positive women preconception and will provide high-quality prospective data on miscarriage rates as well as the efficacy of T₄ treatment in the future (9).

What is the therapeutic evidence for benefits following normalisation of thyroid function during pregnancy?

There are only few outcome data on L-T₄ treatment in SCH, with and without TPO-Ab positivity, during pregnancy.

Amongst the published studies, treatment was initiated at different TSH thresholds; some in subjects with TSH concentrations even lower than the proposed threshold of 2.5 mU/l and others with TSH concentrations >4.5 mU/l. In one study, 984 pregnant women were screened to identify 115 euthyroid pregnancies with normal TSH but with TPO-Ab positive, who were then divided into a T₄-treated group and a control group, recruited at a mean gestation of 10 weeks and followed up until delivery. Mean TSH at the start of the intervention was comparable in the T₄-treated intervention group (TSH 1.6 mU/l; 57 TPO-Ab-positive subjects) and the TPO-positive controls (TSH 1.7 mU/l; 58 TPO-positive subjects), whereas in the TPO-Ab-negative control cohort, TSH was even lower (TSH 1.1 mU/l; *n*=869). The mean T₄ dose was 49.7 µg/day in the intervention group, which resulted in significantly lower TSH levels than that in the TPO-Ab-positive controls. Miscarriage rate was described as significantly lower in the treated group and equivalent to the TPO-Ab-negative controls (45). However, the mean gestational age of starting L-T₄ was estimated to be 10 weeks, and all but one of the miscarriages occurred at <11 weeks.

A Belgian study of TPO-Ab positive, treatment naïve patients which compared them to a T₄-treated group revealed a miscarriage rate of 0/34 in subjects treated with 50 µg/day of T₄ during pregnancy as compared with 5/31 in untreated subjects. Serum TSH levels in both groups were, however, marginally different with a mean of 1.61 mU/l in the untreated group vs 1.05 mU/l in treated participants, albeit all within the normal range (46). In another small prospective, randomised trial in patients undergoing assisted reproduction which included those with slightly higher serum TSH concentrations, who were treated with 50–100 µg T₄/day from preconception (average mean TSH was 1.1 mU/l vs 4.9 mU/l in the untreated control group), the miscarriage rate appeared higher in controls than that in treated patients (47). It has to be borne in mind that the real comparison of miscarriage rate is based on the number of pregnancies achieved, which leaves the study with even lower numbers (three miscarriages out of 12 in the T₄ group vs four out of five control pregnancies). This is in contrast with an investigation in women suffering from recurrent pregnancy loss. Focusing on live birth rates, there was no difference in the outcome between euthyroid patients (*n*=141) and patients with SCH (*n*=39). There was also no difference between treated (*n*=24) and untreated (*n*=15) SCH subjects (48). In a prospective randomised trial of 64 infertile patients with

Position Statement	G Brabant and others	Critical review of subclinical hypothyroidism in pregnancy	173:1	P5
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SCH undergoing controlled ovarian stimulation for IVF/ICSI, a T₄ therapy arm (initial TSH 6.6 mU/l) and a control group (initial TSH 6.7 mU/l) were formed (~80% in both groups were TPO-Ab positive). None of the patients were treated with 50 µg/day T₄, but four of the untreated pregnancies ended in miscarriage, and the embryo implantation rate as well as live birth rate was significantly higher in the L-T₄ treatment group; importantly, the TPO-Ab concentrations were also significantly higher in the control group (49) (for overview of all mentioned studies see Table 1).

There are several studies that shed some light on the impact of TH therapy on pregnancy complication rates, but these studies were not designed to judge the efficacy of therapy on pregnancy outcomes (50). This equally applies to the largest completed prospective study thus far to evaluate the efficacy of T₄ treatment on the neurophysiological outcome in the offspring (CATS trial). This trial evaluated, as a secondary outcome, pregnancy complications in maternal thyroid hypofunction, including SCH (TSH above the 97.5th percentile and/or fT₄ below the 2.5th percentile) before 16-week pregnancy (51). A total cohort of 21 846 women was screened and 1050 (4.8%) fulfilled the study criteria; 404 women were in the untreated control group, whereas 390 received T₄ treatment. As pregnancy-related complications were not the primary outcome of the study, the results published are not detailed in this respect. However, they concluded that 'no significant differences between the screening and control groups were observed with respect to gestational age at delivery (median, 40.1 and 40.2 weeks, respectively;

$P=0.10$), rates of preterm birth (<37-week gestation, 5.6 and 7.9%; $P=0.20$) and birth weight (mean, 3.5 and 3.3 kg; $P=0.15$)'.

Furthermore, treatment with T₄ does not necessarily result in an euthyroid state. A recent, retrospective analysis of 1013 pregnant women on T₄ medication demonstrated that only 37.1% of the patients were within the target range of 0.2–2.5 mU/l, 6.5% overtreated and 56.4% undertreated. The possible impact of miscarriage rates secondary to overtreatment cannot be judged due to the low numbers, but there was a significant association between miscarriage and increased TSH levels above the target TSH range of 0.2–2.5 mU/l. This was largely due to the disproportionate impact of cases where the TSH was >10 mU/l, but significantly increased already when TSH was >4.5 mU/l (52). Similarly, another small study suggested more miscarriages with both suppressed and elevated TSH in pregnant women on T₄ replacement (53).

In summary, all these studies are hampered by the low number of patients, by wide heterogeneity and by the fact that in some studies treatment was initiated despite a seemingly normal TSH concentration at the start of treatment.

Utero-placental unit and TH homeostasis

The utero-placental unit is the maternal–foetal interface that consists of genetically different maternal and foetal cells whose activities are modulated by a complex network of cellular crosstalk involving the local release of hormones, cytokines, chemokines and growth factors.

Table 1 Overview of studies on the effects of thyroxine treatment on miscarriage rate in pregnancy.

Study	Study design	Initial TSH (mU/l) (control vs T ₄)	Dose of thyroxine (µg/day)	Thyroid autoimmunity	Miscarriage rate/ group size (control vs T ₄)	References
Negro <i>et al.</i>	Prospective Randomised	1.7 vs 1.6 at week 10	0 vs 49.7 ± 14	Yes	8/58 vs 2/57	(45)
Lepoutre <i>et al.</i>	Retrospective Non-randomised	1.61 vs 1.05 first trimester	0 vs 50 with dose titration	Yes	5/31 vs 0/34	(46)
Wang <i>et al.</i>	Prospective Non-randomised	> 2.5 before week 12	50–100, not specified	Not reported	26/168 vs 2/28	(47)
Abdel-Rahman <i>et al.</i>	Prospective Randomised	4.8 vs 4.7 IVF T ₄ started before IVF	0 vs 50–100 with dose titration	Not determined	4/5 vs 3/12 ^a	(80)
Kim <i>et al.</i>	Prospective, randomised IVF	6.7 vs 6.6 T ₄ started with stimulation	0 vs 50	Both accepted	4/12 vs 0/17 ^a	(49)

^aThe denominators are the absolute number of pregnancies achieved following IVF.

Position Statement	G Brabant and others	Critical review of subclinical hypothyroidism in pregnancy	173:1	P6
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This is key to preventing immune rejection of the foetus as well as ensuring adequate trophoblast invasion and placentation for effective nutritional and waste exchange. Defects in this delicate network and placentation may lead to pregnancy complications, such as miscarriage, preterm labour, pre-eclampsia and foetal growth restriction. The putative role of THs in this regulation is far from clear, but human data show that a range of TH transporters, TH-binding protein (transthyretin (TTR)), the deiodinases D2 and D3 as intracellular activators and inactivators of THs, as well as TH receptor isoforms, TR α 1, TR α 2, TR β 1, are expressed in the key cellular components forming the placenta. The expression of the receptors increases with gestational age (54). Tri-iodothyronine (T₃) is able to alter the cytokine network in a cell-type and gestational age-dependent manner in human utero-placental cells (55) and promote human trophoblast invasion (56).

Human placental tissue is able to produce TH-binding proteins such as TTR and albumin (57). These binding proteins may play an as yet undefined role in the regulation of TH levels and their vulnerability to placental degradation. The observation that high levels of TTR are present in foetal serum when foetal liver *TTR* mRNA expression is very low may suggest a placental origin (57). The human sodium iodide symporter (NIS) is detectable in villous placental tissue as early as 6 weeks of pregnancy, substantially increases to a peak during the first 12 weeks of pregnancy (58) and may be autoregulated by iodine availability (59).

TH transporters are able to regulate the availability of THs to placental tissue. They are expressed in various placental cell types, but their role in the regulation of placental development itself and the transfer of TH to the foetus are not completely understood. In studies on the microvillous plasma membrane of human term syncytiotrophoblasts, which are in direct contact with the maternal blood system, a wide variety of transporters have been characterised such as L-type amino acid transporter 1 and CD98, monocarboxylate transporter 8 (MCT8) and MCT10, organic anion-transporting polypeptide 1A2 (OATP1A2) and OATP4A1 (60).

It is interesting to note that in the rat, which has a different type of placental system compared with the human, OATP1C1 and MCT8 regulation seem to be affected by nutritional iodine supply (61). Moderate-to-severe iodine deficiency in the rat increases OATP1C1 in the period before the onset of foetal thyroid function (GD16), whereas a downregulation is observed thereafter (GD20). During this latter period MCT8 is upregulated.

Both D2 (involved in the activation of T₄ to T₃) and D3 (responsible for TH degradation) are expressed in placenta (62). Detailed studies in human placenta demonstrate that D3 is expressed in the maternal decidua, the syncytiotrophoblast layer (maternal aspect), the cytotrophoblasts (foetal aspect) and the foetal endothelium of the chorionic villi to control local TH concentrations (52). The expression of deiodinases on the maternal side of the placenta may have consequences also on maternal TH levels as we know from consumptive forms of hypothyroidism that high expression of D3 in tumour tissue may lead to a substantial decrease in TH concentrations even in adulthood (63). According to immunohistochemical studies in human placenta, there is lower D3 expression in cytotrophoblasts compared with syncytiotrophoblasts, whereas D2 expression is more prominent in cytotrophoblasts (64, 65).

High expression of D3 on the maternal side of the placenta is suggested to be more effective in protecting the foetus from exposure to temporally inappropriate concentrations of maternal THs. In addition, changes in the expression and action of multiple TH transporters within the placenta across gestation serve to regulate placental TH uptake and the transplacental passage of TH to the foetus (60, 66). Generally, placental D3 activity is ~200-fold greater than D2 making D3 the predominant deiodinase in placenta (57). Owing to its high degradation activity, D3 has a major impact on the availability of T₃ to its specific receptors.

In mice, D2 is highly expressed in the uterus by days 3–4 of gestation and D3 is significantly induced in uterine stromal tissue immediately following implantation and is closely regulated by progesterone and also by substrate autoregulation where T₃ stimulates D3 activity, suggesting that protection against local T₃ elevations are critical in early pregnancy (62). Mice placental D3 activity decreases across pregnancy whereas D2 is upregulated at GD20 (61). The highest expression of D3 is found in the villous syncytiotrophoblast, suggesting an important function to control for variations in maternal TH concentrations. This is in part reflected in changes in maternal TH concentrations in healthy pregnancy, where levels of reverse T₃ to total T₃ reveal a clear shift with a sharp increase in the ratio from early in pregnancy and throughout pregnancy. The critical importance of TH degradation to protect the foetus from the detrimental effects of high TH levels in early embryonic development has been shown in D3-knockout mice, where offspring develop central hypothyroidism due to thyrotoxicosis in early development (67, 68). For the human, *ex vivo*

placental perfusion studies have demonstrated significant T_4 inactivation by D3 during transplacental passage (69), but data are still too incomplete to draw firm conclusions on the role of deiodinases, especially D3, in the regulation of maternal-to-foetal transfer of THs under normal conditions and in pathophysiological states.

TH concentrations in the offspring

Data on TH concentrations in the foetus during the course of pregnancy are scarce. In humans they are mainly based on blood sampled by cordocentesis. A relatively large study published back in 1991 established TSH and TH reference concentrations in 62 foetuses during the course of pregnancy, including blood obtained by cordocentesis before the 14th week of pregnancy, before endogenous foetal TH production. In all pregnancies, the investigation was performed for a suspected pathology, but only offspring normally developed for their gestational age with minor malformations such as polycystic kidney disease were included. In comparison with the parallel sampled maternal levels, TH concentrations in the foetus are much lower, particularly in the first part of pregnancy along with significantly higher foetal TSH levels (70) (Fig. 1).

The low levels of foetal THs in early pregnancy, confirmed by others, support the discussed high efficacy of placental regulation to optimise circulating TH levels for the foetal demands during the respective stage of pregnancy whilst allowing local activation of THs to satisfy independent spatial and temporal requirements of each tissue depending on the developmental stage (54). The continued transfer of THs from mother to foetus until delivery is exemplified in studies of athyreotic neonates

at birth, which demonstrate that maternal TH transfer occurs and can enable them to reach TH concentrations of ~50% of a normal neonate (71). In cases of intrauterine growth restriction or placental insufficiency, foetal TH levels are described to be lower than that in the reference population (72).

The effect of maternal T_4 treatment on circulating foetal TH concentrations has recently been investigated. In mothers with autoimmune hypothyroidism ($n=25$), the effect of T_4 replacement was monitored by cordocentesis between weeks 22 and 33 of pregnancy (73). Despite treatment to euthyroidism in all but one hypothyroid mother, 60% of the foetuses showed higher than normal fT_4 levels in blood obtained by cordocentesis (74). In another large study of 246 neonates of T_4 -treated mothers with known pre-existing hypothyroidism, both serum fT_4 and TSH concentrations were found to be high within a few days of birth (59). Furthermore, the mean birth weight and head circumference were significantly lower than that in controls ($n=139$). In view of data in healthy euthyroid mothers, where a significant positive correlation was observed between fT_4 concentrations across the normal reference range (in cord blood at birth) and birth weight, these results could be viewed as a problem of insufficient supply with THs during pregnancy (75). On the contrary, it is well known that hyperthyroidism too may lead to foetal growth retardation. This phenomenon is not restricted to autoimmune thyroid dysfunction, but is shown in patients with activating TSH receptor mutations where premature labour and low birth weight are a consistent finding (76). This would fit the results of the recently published, Generation R study, which suggests that high maternal fT_4 during the first trimester is associated with low birth weight indicating a much more complex relationship (77). Moreover, Danish registry studies have shown low birth weights in children born to mothers with hyperthyroidism, and high birth weight in hypothyroidism (78). Currently, we know very little about the effects of maternal T_4 therapy on TH concentrations in the foetus and whether the additional T_4 dosage is indeed transferred through a variably disturbed utero-placental unit.

Summary and perspectives

SCH in pregnant patients is not a clearly defined condition but a disorder in the grey zone between normality and pathophysiology, currently lacking any marker to predict effects on the foetus itself. Considerable efforts have been made to better define this condition, particularly aiming

Figure 1

Maternal and foetal TSH and fT_4 serum concentrations during pregnancy (70).

to identify the timing when therapeutic interventions with THs may be indicated. This has been summarised and formalised for non-pregnant conditions in guidelines from TES, ATA, AACE and most recently the ETA (1, 79). The methodological problems associated with measurements under non-pregnant conditions are accentuated in pregnancy. Thus, establishing a firm diagnosis of the condition may not be trivial in pregnancy. Furthermore, defining firm thresholds for treatment based on thyroid function tests – which is not trivial outside pregnancy – is much more challenging in pregnancy. Measurement of clinical outcomes including miscarriage, stillbirth, long-term cognitive function as well as risk of attention deficit hyperactivity or psychiatric disorders of the offspring require large sample sizes and may be confounded by many factors. Furthermore, the question of whether mild maternal dysfunction is the cause or the consequence of any malfunction of the utero-placental unit, or simply a confounding factor to other primary aetiologies such as an accompanying autoimmune disorder, remains largely open.

Currently, we lack any reliable non-invasive foetal marker to monitor the effects of maternal T₄ therapy in routine clinical practice, except for foetal growth ultrasound scanning, which remains a relatively blunt instrument with poor sensitivity and specificity in this context. Our knowledge of the regulation of the transfer of THs across the utero-placental unit is in its infancy. It appears to be controlled by binding proteins such as TTR, various TH transporters activities, a highly efficient pre-receptor control based on D2 and D3 activities and the expression of different TH receptor subtypes. All of these regulatory mechanisms are currently incompletely understood. Despite these uncertainties, the marked differences between maternal and foetal TH concentrations suggest that the interplay of all these regulatory placental pathways is highly efficient to control foetal TH availability, particularly in the critical first weeks of pregnancy. With the lack of any reliable foetal markers to target T₄ treatment within the framework of a highly regulated, complex barrier system between the maternal and foetal circulation, present data appear to be insufficient to support treatment of all pregnant women with a serum TSH level slightly above 2.5 mU/l. It is too simplistic to expect a general improvement in pregnancy outcomes and neurodevelopment of the offspring based on this criterion. Several large prospective trials in different countries such as the USA, UK and The Netherlands will hopefully help to clarify these questions in the future.

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Position Statement	G Brabant and others	Critical review of subclinical hypothyroidism in pregnancy	173:1	P9
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