REVIEW ARTICLE

Subclinical hypothyroidism and related biochemical entities in pregnancy: implications and management

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Summary: Subclinical hypothyroidism (SCH), thyroid autoimmunity and isolated maternal hypothyroxinaemia are diagnoses made on laboratory findings. The two former conditions are commonly identified in the general population, while the term isolated maternal hypothyroxinaemia was developed to highlight potential neurodevelopmental risks in progeny. Each entity has been associated with either obstetric, perinatal and/or child developmental harm in observational studies, although few interventional trials have been performed to guide diagnostic and therapeutic approaches. Once diagnosed, treatment of SCH is recommended by endocrine groups to limit potential risk, given that harm from appropriate therapy is unlikely. Screening for thyroid disorders in pregnancy has traditionally been controversial. Definitive trials are expected to report over coming years and updated consensus guidelines will hopefully resolve this issue.

Keywords: subclinical hypothyroidism, thyroid autoimmunity, hypothyroxinaemia, pregnancy

INTRODUCTION

Subclinical hypothyroidism (SCH) is a biochemical diagnosis and is defined as an abnormally increased serum thyroid-stimulating hormone (TSH), in the presence of serum free thyroxine (fT4) and triiodothyronine (fT3) levels within their respective reference ranges.[1] SCH is common in the community, especially in those over 65 years of age.[2] In the general population, reported associations include neuropsychiatric manifestations, impaired cardiovascular function and lipid abnormalities, although their clinical significance is uncertain.[1] As a result, opinions vary on treatment and screening recommendations.[3,4] Endocrine but not obstetric groups agree on the requirement for treatment of identified SCH before and during pregnancy.[2,5] As such, this issue as well as screening has been the subject of intense interest and debate since the late 1990s. Not all questions have been resolved, although new data emerging may allow more definitive recommendations within the next few years. This review assesses the current state of knowledge on SCH and related concepts of thyroid autoimmunity and isolated maternal hypothyroxinaemia, including issues of screening for thyroid dysfunction in pregnancy.

THYROID HORMONE AND THYROID FUNCTION IN PREGNANCY

The thyroid is important in normal reproduction, both prior to and during pregnancy. Severe thyroid dysfunction impairs fertility by impairing ovulation.[6] Circulating maternal thyroid hormone not only serves the mother, but also the fetus. Maternal thyroid hormone (principally fT4) is the major source of fetal thyroid hormone until significant fetal production commences near mid-gestation.[7]

Physiological changes in normal pregnancy (Box 1) mandate an increase in thyroid hormone production of approximately 50% to maintain adequate serum levels.[8] Goitre formation is common, especially in iodine-deficient regions, although gland enlargement by 10–20% occurs even in areas of iodine sufficiency.[9] Thyroid hormone requirements increase in hypothyroid women relying on exogenous thyroxine. These women require an average of 25–50% increased dose by the end of pregnancy,[10–12] with an increment measurable by the fifth week of gestation.[12]

Under these physiological conditions and the influences described below, the measurable hormones of the hypothalamic–pituitary–thyroid axis vary throughout pregnancy. TSH is the most sensitive marker of thyroid status, with lowest levels typically seen in the first trimester.[13] Gestational age-specific reference ranges have been reported, allowing the possibility of more accurately diagnosing subtle thyroid dysfunction.[14,15] Other factors impacting on TSH levels include race,[15,16] multiple pregnancies, thyroid autoimmunity and iodine status.[13] Thyroid autoimmunity (even when initially euthyroid) leads to a fall in fT4 and rise in TSH as pregnancy progresses. This may be subtle and on average all indices remain within the normal range.[17]

The importance of adequate iodine intake in pregnancy has been well established, especially with regard to fetal neurodevelopment.[18] Maternal iodine losses (Box 1) mandate increased iodine intake. The initial and major change in thyroid function tests related to iodine deficiency is relative

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Box 1 **Physiological changes in pregnancy leading to increased thyroid hormone production**

Thyrotropic activity of βhCG in the first trimester
TBG elevation due to increased synthesis and prolonged half-life by altered glycosylation (secondary to oestradiol)
Accentuated maternal iodine losses secondary to augmented maternal glomerular filtration and placental iodine transfer
Transplacental passage and metabolism of thyroid hormone

TSH = thyroid-stimulating hormone; βhCG = β human chorionic gonadotrophin; TBG = thyroxine-binding globulin

hypothyroxinaemia.[19] While urinary iodine excretion is a valid population indicator of iodine sufficiency, a diagnostic test for individual patients remains elusive.[18] The World Health Organization recommends a daily intake of 250 μg throughout pregnancy and lactation, and promotes the approach of universal salt iodization as the most effective method of preventing iodine deficiency disorders.[20] Other approaches, including that of Australia and New Zealand, advocate fortification of foodstuffs such as bread,[21] while adventitious addition of iodine to milk occurs in some countries.[18] Single product fortification may not be adequate for the requirements of pregnancy; specific supplementation (for example products containing 150 μg iodine) is advised where universal salt iodization does not occur.[21]

DEFINITION AND PATHOPHYSIOLOGY OF HYPOTHYROID DISORDERS

SCH, overt hypothyroidism (OH), isolated maternal hypothyroxinaemia and thyroid autoimmunity are defined in Box 2. Isolated maternal hypothyroxinaemia is the only one peculiar to the obstetric setting.

The epidemiology of SCH in pregnancy is reasonably well defined. Most studies have estimated the prevalence to be 2.2–2.5%.[22–25] The upper limits of normal TSH reference ranges used to define SCH differed between the studies (range 2.5–6 mU/L). These methodological differences potentially have a major bearing on the prevalence. Occasionally, studies have found higher rates of TSH above their reference thresholds.[26,27] The rates of OH during pregnancy are much lower, in the order of 0.2–0.3%.[23,24]

In the absence of iodine deficiency, thyroid autoimmunity is the most common cause of hypothyroidism in women of reproductive age. Thyroid autoimmunity is defined by antibody status in studies, although antibodies are not always positive, even in cytology-proven cases of lymphocytic thyroiditis.[28] Nevertheless, the high correlation between positive antibody status and abnormal thyroid function in obstetric studies supports the role of thyroid autoimmunity in hypothyroidism in pregnancy.[24,25,29]

Box 2 **Definitions**

SCH
Serum fT4 and fT3 levels within their respective reference ranges in the presence of abnormally increased serum TSH level*
OH (primary)
Serum fT4 and/or fT3 levels below their reference range in the presence of abnormally increased serum TSH level*
Isolated hypothyroxinaemia
Serum fT4 below the normal reference range in the presence of normal TSH level*
Thyroid autoimmunity
Presence of anti-TPO and/or anti-Tg antibody in the serum, without or without thyroid function disturbance

SCH = subclinical hypothyroidism; OH = overt hypothyroidism; TPO = thyroid peroxidase; Tg = thyroglobulin
*In pregnancy gestational age-specific TSH reference ranges should be used

EVIDENCE OF HARM SPECIFIC TO SCH

OH is associated with an increased risk of obstetric problems, including infertility,[6] spontaneous abortion, hypertensive disorders of pregnancy, placental abruption, fetal distress, preterm birth, low birth weight and perinatal death.[7] The major question is whether more subtle degrees of thyroid dysfunction also cause harm.

SCH and fertility

The relationship between OH and infertility is well known; an association between SCH and infertility is much more questionable. A review of this subject observed that most studies were poorly controlled and thus there was no good evidence supporting such a claim.[30] For those undergoing assisted reproductive technologies, a recent trial found that treatment of SCH with thyroxine did produce measurable benefits in clinical pregnancy, miscarriage and delivery rates.[31]

Fetal neurodevelopment

Inadequately treated maternal hypothyroidism and impaired fetal neurological development were first linked in studies commenced in the 1960s,[32–34] although accumulation of further clinical data took decades.

Haddow *et al.*'s[35] study published in the *New England Journal of Medicine* in 1999 caused an explosion of interest, and remains influential today. This paper described a retrospective case control study of 62 singleton offspring identified on the basis of their mother's TSH levels measured in the second trimester. This paper has subsequently been cited as a study of offspring of patients with SCH; however, it is likely that most mothers had (at least) biochemical OH, because for the 18 mothers with the mildest elevations in TSH, the selection criteria also included a low total thyroxine (TT4) level. The children underwent neuropsychological evaluation between the ages of seven to nine and the mean intelligence quotient (IQ) of offspring from the untreated women ($n = 48$) was seven points lower than controls. A much larger proportion (19% versus 5%) of offspring in the untreated hypothyroid group had an IQ <85 compared with controls. The offspring of the treated but still hypothyroid women ($n = 14$) showed no difference to the controls; the researchers hypothesized that these women were euthyroid in early pregnancy at a time when maternally derived thyroxine might be important.[36] A follow-up paper suggested an inverse gradient between severity of maternal hypothyroidism and offspring IQ.[37]

Subsequent observational studies addressing SCH have given mixed results,[27,38–40] although interpretation is hampered by small samples and short follow-up in most studies, and the retrospective design of one. A small prospective study assessed eight women with SCH who were identified early in pregnancy and treated to euthyroidism. No

neurodevelopmental differences were found in offspring at nine months of age compared with controls.[38] This of course does not answer the question of whether there was any increased risk at all to begin with. Another small prospective study using Bayley Developmental Index scales found a lower mental Development Index at one year of age in offspring of SCH mothers, although this became non-significant at two years of age and other indices were not affected by thyroid status.[39] The relationship of maternal thyroid function to offspring's neurodevelopment was assessed prospectively in a New England cohort of 500 women.[27] No association was found with childhood cognitive test scores at age six months and three years. A case control study from China found a statistically significant difference in mean motor and mental Bayley Developmental Index scores between offspring born to SCH mothers and euthyroid controls when assessed between 25 and 30 months of age.[40]

Obstetric and perinatal risks

Both small single-centre series and larger observational cohorts have addressed the question of obstetric and perinatal risk of SCH. A single screening and intervention study has recently been published (discussed later).[22]

Most series support the concept that SCH is associated with fewer complications than OH,[41–43] although one did conclude it was not so much the initial severity of hypothyroidism but the adequacy of replacement that determined complications.[44]

The largest obstetric outcomes study assessed over 17,000 subjects and found SCH to be associated with preterm birth, its neonatal complications (including respiratory distress and intensive care admission) and placental abruption.[23] Two other large studies have also identified an increased risk of adverse outcomes. One determined a continuous relationship between rising TSH and pregnancy loss (which included either miscarriage, fetal or neonatal death),[45] while another found an elevated risk of fetal death.[25] However, several other sizeable cohort studies did not identify any added risk of adverse outcomes for either fetus or mother.[46–48]

Postpartum issues

In the year following delivery, postpartum thyroiditis (PPT) is common, with an estimated prevalence of 8.1%.[49] Most published studies have not specifically addressed women with previously diagnosed thyroid function abnormalities such as SCH. Given the common aetiological role of thyroid autoimmunity in PPT and SCH, an association between them would not be surprising. One report observed a discrepancy between prepregnancy levothyroxine replacement for hypothyroidism and postpartum dosing, suggesting that flares in autoimmunity can affect those with documented thyroid function abnormalities.[50] For those who do experience PPT, depressed mood may be a prominent feature, in addition to other symptoms of overt thyroid dysfunction.[51] There is currently insufficient evidence to conclude whether an aetiological link exists between the two conditions.[52]

Screening for PPT has been addressed by the Endocrine Society guidelines.[52] These suggest TSH measurement at three and six months postpartum for women with positive thyroid peroxidase (TPO) antibodies, type 1 diabetes or post-partum depression. Annual TSH determination is also recommended in women following PPT.

Regarding long-term risk, a cohort study with 20-year follow-up found subsequent thyroid disease to be the only sequela associated with gestational SCH.[47] Following PPT, long-term risk of hypothyroidism appears high, with a recent longitudinal study finding a prevalence of 36% at 12 years, compared with 4% of women who did not have PPT.[53]

RISK ASSOCIATED WITH MATERNAL HYPOTHYROXINAEMIA AND AUTOANTIBODY STATUS

No discussion of subtle thyroid abnormalities in pregnancy can ignore isolated maternal hypothyroxinaemia or autoimmunity, because harm has also been independently attributed to these laboratory diagnoses, and both could also become targets for screening or case finding strategies.

Isolated maternal hypothyroxinaemia

Isolated maternal hypothyroxinaemia is a diagnostic construct whose origins can be traced to the fetal neurodevelopmental debate. Aside from the observation that those with iodine deficiency tend to develop relative hypothyroxinaemia preferentially to elevated TSH,[19] there is no known aetiology to account for isolated maternal hypothyroxinaemia, and in most situations it is probably a normal variant without maternal harm. However, maternal thyroxine is the only source of fetal thyroid hormone in early pregnancy, and it is biologically plausible that low maternal fT4 levels (whether or not TSH is also raised, and independent of iodine deficiency) could lead to inadequate transfer of thyroxine to the developing fetus.[54]

The first study to report an association between isolated maternal hypothyroxinaemia and adverse fetal outcome was performed on an iodine-sufficient population within The Netherlands.[55] (Note: while Man's studies from the 1960s[32–34] may well have included women with isolated hypothyroxinaemia, the proportion of women with OH can't be ascertained because her work pre-dated modern TSH assays.) In this study, the 22 children born to mothers with fT4 below the 10th percentile at 12 weeks gestation were found to have lower psychomotor (but not mental) Bayley Developmental Index scores at 10 months of age, compared with the rest of the cohort. The same group undertook a second similar but larger study with slightly longer follow-up.[56] Here the 57 offspring of women below the lowest 10th percentile for fT4 at 12 weeks gestation had both lower motor and mental Bayley Developmental Index scores at one and two years of age. When subanalyses of the groups were undertaken, only offspring whose mothers were those with persistently low fT4 levels at 24 and 32 weeks gestation had lower scores. This runs counter to the concept of the critical period in early gestation, but is potentially reassuring in that it could allow beneficial intervention following screening performed in early gestation.

Only two other published studies undertaken in iodine-sufficient populations have attempted to confirm a link between maternal fT4 levels and neurological outcomes, with mixed results. One found no link,[27] while another reported

an association (this study also found SCH and thyroid antibody status to be independent negative predictors of outcome).[40]

It is difficult to make firm conclusions on the maternal hypothyroxinaemia literature. Each study was small and the longest follow-up of offspring was three years; thus the persistence of any putative effect is unclear. Secondly, measured fT4 levels are sensitive to the abnormal protein binding state of pregnancy and TT4 methods are much more accurate, although not widely available.[13] Therefore, correct patient selection for targeted intervention may be difficult to achieve. Furthermore, isolated maternal hypothyroxinaemia does not appear to have any consistent effect on obstetric or perinatal complications,[45,48,57] limiting the indication for therapy to putative neurodevelopmental protection alone.

Thyroid autoimmunity

Autoimmune thyroid disease is the most common autoimmune disorder (affecting 5–10% of women of reproductive age), as well as being the most common cause of hypothyroidism.[58]

No clear association has been demonstrated between infertility and thyroid antibody status, with varying study designs and variable results making interpretation difficult.[30]

A rich literature exists for the association of maternal thyroid autoimmunity (even in the presence of normal thyroid function tests) and miscarriage.[30,59] One randomized intervention study described significant reductions in miscarriage and premature delivery to baseline population levels with low-dose levothyroxine.[17] This provides evidence for the role of subtle thyroid dysfunction caused by a limited thyroid reserve playing a causative role in complications. Thyroid autoimmunity has also been identified to be associated with higher perinatal mortality in one study.[46]

On the question of fetal neurodevelopment, studies have yielded varying conclusions.[27,40,60] A prospective Dutch study investigating the relationship between thyroid autoimmunity and postpartum depression unexpectedly found that positive maternal antibody status was associated with significantly poorer cognitive scores in the 19 affected offspring (out of 230) at age five years.[60] A subsequent study by the same group did not find TPO antibody status to be an independent predictor of infant neurodevelopment on multiple regression analysis.[55] No such relationship was found in a study of 500 New England children tested at age six months and three years.[27] A Chinese case control study including 34 TPO-positive women found lower cognitive scores among children of cases at age 25–30 months.[40]

CONSENSUS MANAGEMENT OF SCH IN PREGNANCY

There is consensus among endocrine groups that once diagnosed, SCH should be treated in pregnancy.[3,4,52,61,62] These groups consider that the potential benefits of judicious levothyroxine use outweigh the small risks, even in the absence of hard interventional data. The American College of Obstetricians and Gynecologists takes the opposite view; in its most recent Committee Opinion it recommends treatment only in the case of OH.[5]

For women with pre-existing thyroid dysfunction, the United States Endocrine Society guidelines suggest aiming for a preconception TSH within the normal range and not higher than 2.5 mU/L, in order to fit within the published gestational age-specific reference ranges.[52] Women currently taking levothyroxine should increase their dose by approximately 30% once they are aware of being pregnant.[12] For those diagnosed in pregnancy, the upper suggested TSH target is 2.5 mU/L within the first trimester, or 3 mU/L in later pregnancy. There are no definitive rules for levothyroxine dose commencement in SCH, although 50–100 μg/day would be reasonable in the majority. Monthly to six-weekly monitoring of thyroid function tests is advised.[52]

UNIVERSAL SCREENING VERSUS CASE FINDING

Universal thyroid function screening in pregnancy remains controversial. Based on the observational neurodevelopmental data, a number of consensus statements have been produced supporting screening.[4,62] Others have been more cautious, suggesting further data are required before blanket recommendations are made.[3,5,52,61,63] The current Endocrine Society guidelines advocate an aggressive case finding approach, using the clinical and laboratory risk factors outlined in Box 3.

The results of the first screening trial, conducted in Southern Italy, were recently published in the *Journal of Clinical Endocrinology & Metabolism*.[22] The study compared universal first trimester screening with a case finding approach similar to the Endocrine Society guidelines, using a hypothyroid case definition of TSH greater than 2.5 mU/L with positive TPO antibodies. Low-risk women in the case finding group had their TSH values measured but not disclosed to treating clinicians, while abnormalities in the screening group were identified and the women treated. High-risk women with thyroid function abnormalities in both the screening and case finding groups were identified and treated. Out of 4562 patients, 133 (2.9%) were found to have abnormal thyroid function. The low-risk women with high TSH and positive antibodies in the screening group (who were identified and treated) had significantly lower combined adverse events than similar low-risk women in the case finding group. However, the primary outcome measure of total adverse events between case finding and screening groups were not different. This was attributable to 95% of adverse events occurring in women without thyroid function abnormalities (97.1% of women). Furthermore, in the 2.9% of patients with abnormal thyroid function, those initially considered high risk had been randomized almost equally to either the screening or case finding arms. Therefore, a positive overall result would have relied on the ~2% of patients treated differently between the groups. Despite the negative primary outcome, the trial can be

Box 3 Current Endocrine Society guidelines for case finding in pregnancy

- Personal history of thyroid disorders
- Family history of thyroid disorders
- Personal history of autoimmune disorders (including type 1 diabetes)
- Personal history of infertility
- Personal history of head or neck irradiation
- Personal history of miscarriage or preterm delivery
- Symptoms or signs suggestive of thyroid disorder (including goitre)
- Laboratory abnormalities suggesting thyroid disorder (including anaemia, hypercholesterolaemia or hyponatraemia)
- Thyroid autoantibody positive

Adapted from ref. 52

viewed as a success for screening, as it showed that identification and treatment of thyroid function abnormalities in low-risk women reduced adverse pregnancy outcomes by nearly 40%, equating to a number-needed-to-screen of 40.[64] Difficulty in demonstrating a primary outcome measure of overall population benefit in a screening trial is not unique to this study; the concept of high noise-to-signal ratio in screening trials means that most are reported in terms of disease-specific outcomes (for example, breast cancer mortality in a mammogram trial rather than overall mortality).[65]

The question remains: is screening worthwhile? Certainly the above screening study hints that obstetric and perinatal adverse events might be decreased in the target population, but requires confirmation. Should neurodevelopmental consequences of SCH and a protection with treatment be confirmed and added to an obstetric benefit, the case for screening would seem overwhelming. The potential harms of screening appear low but could include excessive levothyroxine treatment and the anxiety related to gaining a disease label. Financial costs of investigation and therapy must also be considered. To date, only one cost-effectiveness study has addressed this issue. It suggested benefit to screening, although its baseline assumption was of neurodevelopmental improvements, and it did not address merits of case finding versus screening.[66]

Other practical issues need to be considered when comparing universal screening to the currently recommended approach of case finding. Current case finding approaches lead to substantial numbers of patients who might benefit from intervention being untreated (estimated percentages depend on the particular case and case finding definitions although the literature ranges from 30% to 75%).[22,67] Given that most clinicians undertaking early pregnancy assessment will not be endocrinologists or obstetric physicians, there is also concern that case finding guidelines may not be followed or that providers may not even be aware they exist.[68,69] Complex case finding rules (such as Box 3) may well limit uptake of guidelines in practice.

The other important dilemmas are what case definition for SCH to use and when to test. A simple TSH threshold is attractive, although no empirical evidence currently exists to support this. TSH combined with antibody status was the criterion in the above-described screening trial, but blanket antibody testing would add to costs and complexity of assessment. Evidence of autoimmunity alone is the other strategy with empirical support, albeit from a small, single-centre study.[17] Ideally assessment would occur prior to conception, although this is clearly not practical for all cases. We simply do not know whether earlier testing would improve outcomes. Thus recommendations would require a large degree of expert consensus, based on currently available evidence.

The authors suspect that the question will eventually be resolved in favour of universal screening, although we believe that the above issues need resolution before this recommendation can be confidently made. Over the coming years further screening and intervention trials are scheduled for completion, including those that will assess neurodevelopmental outcomes and isolated maternal hypothyroxinaemia.[40,70,71] Hopefully these and updated consensus guidelines from representative societies will provide sufficient clarity.

CONCLUSIONS

SCH and related biochemical entities are laboratory diagnoses, by definition at the lower end of a spectrum of thyroid dysfunction. There are potential harms to both mother and developing fetus, although at present few prospective randomized interventional studies have been completed to confirm observational data. Consensus guidelines from endocrine groups suggest treatment of SCH once diagnosed. Universal screening remains controversial, though we consider that the pendulum is swinging in this direction. Definitive answers may be available over coming years.

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