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STATE OF THE ART REVIEW

Diagnosis and management of subclinical hypothyroidism in pregnancy

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ABSTRACT

In prospective studies, the prevalence of undiagnosed subclinical hypothyroidism in pregnant women ranges from 3% to 15%. Subclinical hypothyroidism is associated with multiple adverse outcomes in the mother and fetus, including spontaneous abortion, pre-eclampsia, gestational hypertension, gestational diabetes, preterm delivery, and decreased IQ in the offspring. Only two prospective studies have evaluated the impact of levothyroxine therapy in pregnant women with subclinical hypothyroidism, and the results were mixed. Subclinical hypothyroidism is defined as raised thyrotropin combined with a normal serum free thyroxine level. The normal range of thyrotropin varies according to geographic region and ethnic background. In the absence of local normative data, the recommended upper limit of thyrotropin in the first trimester of pregnancy is 2.5 mIU/L, and 3.0 mIU/L in the second and third trimester. The thyroid gland needs to produce 50% more thyroid hormone during pregnancy to maintain a euthyroid state. Consequently, most women on levothyroxine therapy before pregnancy require an increase in dose when pregnant to maintain euthyroidism. Ongoing prospective trials that are evaluating the impact of levothyroxine therapy on adverse outcomes in the mother and fetus in women with subclinical hypothyroidism will provide crucial data on the role of thyroid hormone replacement in pregnancy.

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Introduction

The past 20 years have witnessed a dramatic increase in the understanding of the interaction between the thyroid gland and pregnancy, and its impact on adverse events in the mother and fetus. In particular, our understanding of how to interpret thyroid function results during pregnancy, as well as the prevalence of subclinical hypothyroidism, its impact, and the best way to treat it, have improved. Pregnancy is a stress test for the thyroid. The thyroid gland must produce 50% more thyroid hormone for euthyroidism to be maintained and to provide enough thyroid hormone for the developing fetus. Simultaneously, the physiological changes that accompany pregnancy result in marked alterations in the normal range of thyroid function. Specifically, human chorionic gonadotropin, which peaks in the first trimester, crossreacts with the thyrotropin receptor, resulting in an upper limit of normal of thyrotropin of 2.5 mIU/L during the first trimester.[1-4]

The most dramatic recent findings have been the association between subclinical hypothyroidism during pregnancy and multiple negative outcomes in the mother and the fetus, including spontaneous abortion, gestational hypertension, gestational diabetes, pre-eclampsia, preterm delivery, and decreased IQ in the offspring.[5-7]

The increased prevalence of thyroid dysfunction in pregnancy and the need for proper management to reduce obstetrical and neonatal adverse events led the American Thyroid Association (ATA) and the Endocrine Society (ES) to release specific guidelines.[8 9]

The current review provides a summary of the above, recommendations for the diagnosis and treatment of subclinical hypothyroidism, and a discussion of the pros and cons of universal screening for thyroid disease during pregnancy. It concludes with a description of prospective ongoing trials.

Definition of subclinical hypothyroidism

Subclinical hypothyroidism is defined as the combination of a raised thyrotropin concentration and normal serum thyroxine (either total thyroxine or free thyroxine). In theory, the diagnosis of subclinical hypothyroidism does not contain an upper thyrotropin limit as long as thyroxine remains within

SOURCES AND SELECTION CRITERIA

We created a list of all relevant topics related to subclinical hypothyroidism in pregnancy and then performed a comprehensive literature review, carrying out a systematic PubMed and Medline search for original articles, reviews, and guidelines published from 1990 to February 2014. Primary papers published before 1990 that were seminal in the field were also analyzed. The search terms used were thyrotropin, levothyroxine, pregnancy, subclinical hypothyroidism, adverse effects, abortion, miscarriage, iodine, thyroid antibodies, and Hashimoto's thyroiditis. We prioritized randomized controlled trials, meta-analyses, and important studies in the field.

Thyrotropin reference ranges in different populations

Reference	Population	Thyrotropin reference range (mIU/L)		
		1st trimester	2nd trimester	3rd trimester
Stagnaro-Green[8]	US*	0.1-2.5	0.2-3.0	0.3-3.0
De Groot[9]	US†	0.1-2.5	0.2-3.0	0.3-3.5
Yan[19]	Chinese	0.03-4.51	0.05-4.50	0.47-4.54
Li[20]	Chinese	0.14-4.87		
Marwaha[21]	Indian	0.6-5.0	0.44-5.78	0.74-5.7
Korevaar[22]	Mixed (Dutch, Moroccan, Turkish, Surinamese)	0.06-4.51		

*American Thyroid Association guideline recommendations.
†Endocrine Society guideline recommendations.

the reference range. However, The ATA, ES, and American Association of Clinical Endocrinologists (AACE) have recommended and generally accepted that any pregnant woman with thyrotropin above 10.0 mIU/L and normal free thyroxine should be diagnosed with overt hypothyroidism.[8-10] Subclinical hypothyroidism is a biochemical diagnosis and cannot be based on the patient's symptoms because these are non-specific and often mimic some of the normal symptoms that a woman experiences during pregnancy.[11]

Thyrotropin and free thyroxine ranges in different trimesters

The normal reference ranges of thyrotropin and free thyroxine differ markedly during pregnancy from those seen in non-pregnant women. To complicate interpretation further, thyrotropin and free thyroxine are significantly different in each of the three trimesters, so that reference ranges need to be trimester specific. It is therefore imperative to use pregnancy derived normal ranges to avoid misdiagnosing a significant number of euthyroid pregnant women as having thyroid disease.[12]

Factors that alter thyroid function during pregnancy include the thyrotropic action of human chorionic gonadotropin, increased iodine renal clearance, raised concentrations of serum thyroxine binding globulin (TBG), and inner ring placental deiodination of thriiodothyroinine and thyroxine.[13-17] Multiple studies have shown that in iodine replete areas, thyrotropin values decrease during the first trimester, whereas concentrations progressively increase during the second and the third trimesters. By contrast, thyroxine is highest in the first trimester and decreases as pregnancy progresses.[18]

The ATA 2011 and the ES 2012 guidelines recommend that the normal thyrotropin reference range should be 0.1-2.5 mIU/L, 0.2-3.0 mIU/L, and 0.3-3.5 mIU/L in the first, second, and third trimesters of pregnancy, respectively.[8 9] However, these reference ranges are probably not valid worldwide, because recent publications indicate that values vary with geographic region and ethnic origin.

Thyrotropin and free thyroxine ranges in different countries

Studies from China and India, for example, reported a significantly higher thyrotropin reference range for each trimester (table).[19-21] Specifically, the normal first trimester range in Chinese women was reported as 0.12-5.08 mIU/L. Use of the ATA 2011 and the ES 2012 guidelines would have resulted in 28% of pregnant Chinese women being diagnosed as having subclinical hypothyroidism versus 4% if the ethnic specific reference range had been used.[20] This study also found that only 30.0% and 20.3% of the 118 pregnant women who had serum thyrotropin greater than 2.5 mIU/L in the first trimester had a value greater than 3.0 mIU/L at the 20th and 30th week of gestation, respectively.

The Generation R prospective cohort study of 3944 people used a 2.5 mIU/L cut-off point as the upper limit of thyrotropin. It reported a marked difference in the prevalence of subclinical hypothyroidism between four ethnic groups—people of Dutch (15.5%), Moroccan (2.7%), Turkish (10.8%), and Surinamese (17.9%) origin. In addition, when population based or ethnicity specific reference ranges were compared, the diagnosis changed in 18% of women initially diagnosed with abnormal thyroid function.[22]

Measurement of free thyroxine

Intrinsic to the definition of subclinical hypothyroidism is that serum thyroxine falls within the trimester specific reference range. However, the diagnosis of subclinical hypothyroidism during pregnancy is complicated by doubts about the accuracy of the standard thyroxine immunoassay during pregnancy. Some investigators have concluded that increased serum TBG concentrations and reduced albumin interfere with the results and decrease the utility of this assay during pregnancy.[23] However, others have concluded that the accuracy of the assay is satisfactory.[24]

As an alternative, dialysate or ultrafiltrate using online solid phase extraction-liquid chromatography-tandem mass spectrometry, has been recommended as the gold standard.[23] However, this technology is expensive, technically demanding, and is not available in most clinical laboratories.

Because of the lack of consensus regarding the optimal technique for measuring free thyroxine during pregnancy, alternative strategies have been proposed. The first alternative is to multiply the non-pregnant total thyroxine reference range (50-150 nmol/L or 3-8.8 µg/dL) by 1.5. The second, the so called free thyroxine index, which has been shown to be reliable during pregnancy, is based on two estimates, the thriiodothyroinine resin uptake and the total thyroxine assay.[9] Unfortunately, no trimester specific reference intervals are available for the free thyroxine index. Furthermore, many laboratories no longer measure total thyroxine, which limits the use of this index.

Using the standard immunoassay during pregnancy, retrospective studies have indicated that the lower free thyroxine concentration (2.5th centile) is about 10.3 pmol/L (0.8 ng/dL) in the first trimester.[18 25-28] However, given the limitations of the free thyroxine assay, the ATA 2011 and the ES 2012 guidelines suggest that, whenever feasible, the reference range for thyroid function tests during pregnancy should be assessed on a local basis, assuming that daily iodine intake is adequate.

A comparison of two longitudinal prospective cohort studies showed the importance of using local reference ranges. Different immunoassays were used to measure thyrotropin and free thyroxine in two separate Danish cohorts of healthy pregnant thyroid antibody negative women. Although thyrotropin values were comparable between the different assays and cohorts, highly significant differences in free thyroxine were seen between cohorts. Specifically,

use of the gestational age specific range for free thyroxine from one cohort resulted in misclassification of all free thyroxine values in the other cohort.[29]

In summary, thyrotropin and thyroxine concentrations change throughout the three trimesters of pregnancy and probably differ by both ethnic group and geographic area. When feasible, local reference ranges should be used. However, most clinicians will not have access to such a laboratory. Consequently, clinicians should use the published thyrotropin reference range that is most appropriate for their geographic area and ethnic origin of their patients.

Causes of hypothyroidism

The leading cause of hypothyroidism in developing countries is severe iodine deficiency, whereas in developed countries it is autoimmune thyroiditis. Thyroid autoantibodies are detected in about half of pregnant women with subclinical hypothyroidism and in more than 80% with overt hypothyroidism.[30] Antibodies directed against thyroid peroxidase (TPO-Ab) should therefore be measured in patients with subclinical hypothyroidism to establish a diagnosis of autoimmune thyroid disease.[8-10]

Although only positive TPO-Ab tests have been shown to be significantly associated with hypothyroidism, antibodies to thyroglobulin (TG-Ab) should also be measured.[31] In a study of 992 unselected women who consulted a tertiary referral center for infertility, the overall prevalence of autoimmune thyroid disease was 16%. Of these women, 8% had both antibodies, 5% had TG-Ab only, and 4% had TPO-Ab only. Women with isolated TG-Ab had significantly higher serum thyrotropin concentrations than those without autoimmune thyroid disease.[32]

If thyrotropin concentrations are raised, TPO-Ab should be measured to establish a diagnosis of autoimmune thyroid disease. If TPO-Ab are present, the measurement of TG-Ab should be considered. Finally, it is important to realize that because the immune system is suppressed during pregnancy, thyroid antibody titers decrease on average by 60% in the second half of pregnancy.[4] Consequently, in some women with autoimmune thyroid disease, thyroid antibody test will be negative during pregnancy but positive postpartum because the immunosuppression of pregnancy yields to an immunologic rebound during the first six months postpartum.

Prevalence of subclinical hypothyroidism

Estimates of the prevalence of subclinical hypothyroidism in the first trimester of pregnancy vary. Initially, this variation was the result of early studies using a non-pregnancy specific upper limit of normal range (4-6 mIU/L) rather than the current definition of 2.5 mIU/L as set by the ATA 2011 and ES 2012 guidelines.[30]

Although most recent studies performed in the United States have shown a 2-3% prevalence of subclinical hypothyroidism when using a thyrotropin cut off of 2.5 mIU/L, a large study published in 2012 reported a prevalence of 15.5% using an upper limit of normal of 2.75 mIU/L.[27 33-37] Similarly, studies conducted outside the US and those that have included various ethnic groups report levels of subclinical hypothyroidism in excess of 15% when using the ATA 2011 and ES 2012 guidelines.[20 38 39]

Even studies within the same country among different ethnic groups have found a great variation in prevalence.[22] These discrepancies are probably the result of different daily intakes of iodine, varying prevalence of thyroid autoimmunity, genetic background, and environmental factors. The marked variation in the thyrotropin range distribution seen in the literature supports the ATA 2011 and ES 2012 recommendation that during pregnancy a trimester specific reference range should be established on a local basis.

Iodine deficiency in pregnancy

During pregnancy, the iodine requirement increases by about 50% because the woman needs to produce more thyroid hormone, renal loss of iodine is exacerbated by the increased glomerular filtration rate, and the fetus needs to produce thyroid hormone during the second half of pregnancy.[15-17] The contribution of iodine deficiency to thyroid insufficiency depends on the severity of iodine deficiency, and inadequate iodine intake is seen in both developing and developed countries.[40] In 2011, nearly 45% of Europeans, including pregnant women and those of child bearing age, were estimated to be iodine deficient.[41]

Although the deleterious effects of severe iodine deficiency on fetal development have been studied extensively, less is known about the impact of mild to moderate iodine insufficiency.[42] The Avon Longitudinal Study of Parents and Children confirmed the central role that maternal iodine status plays in the development of childhood cognition.[43] This British study assessed IQ at age 8 years (Wechsler intelligence scale for children) and reading speed, accuracy, and comprehension (Neale analysis of reading ability) at age 9 years in 7408 children. Each mother's urinary iodine concentration was measured in stored samples from the first trimester (≤13 weeks' gestation; median 10 weeks). Iodine to creatinine ratios were dichotomized on the basis of World Health Organization criteria for iodine deficiency or sufficiency in pregnancy (<150 µg/g or ≥150 µg/g). The results showed that after adjustment for confounders, children of women with an iodine to creatinine ratio less than 150 µg/g were more likely to have scores in the lowest quartile for verbal IQ, reading accuracy, and reading comprehension than children of mothers with ratios 150 µg/g or more. Moreover, when the less than 150 µg/g group was subdivided, scores worsened progressively in the less than 150 µg/g, 50-150 µg/g, and less than 50 µg/g subgroups.

A Spanish study showed that children whose mothers had received an iodine supplement of 300 µg had a more favorable psychometric assessment than those who had not (higher scores on the psychomotor development index (P=0.02) and the behavior rating scale).[44]

These data highlight the importance of adequate iodine status during early gestation. They also emphasize the risk of iodine deficiency even in developed countries and the need for randomized placebo controlled trials to test the effect of maternal iodine supplementation on child cognition.

The National Health and Nutrition Examination Survey (NHANES) has documented a marked decrease in the median urinary iodine concentration over the past three decades, with the current value for pregnant women being 125 µg/L, indicating that pregnant women in the US are

Author	Year	Country	SCH (n)	Study type	Trimester	Definition of SCH*	Miscarriage	Fetal death	Preterm delivery	Gestational diabetes	Hypertension	Eclampsia	Placental abruptio	Low birth weight
Leung[53]	1993	US	45	Retrospective		>5.0	○	○	○	○	●	○	○	○
Allan[30]	2000	US	209	Retrospective	2nd	>6.0	○	●	○	○	○	○	○	○
Casey[34]	2005	US	404	Prospective	2nd	2.74-5.09	○	○	●	○	○	○	●	○
Cleary-Goldman[27]	2008	US	240	Prospective	1st and 2nd	4.0 and 4.3	●	○	●	●	●	●	●	○
Männistö[36]	2009	Finland	224	Prospective	1st	>3.6	●	●	●	○	○	○	○	●
Sahu[39]	2010	India	41	Prospective	2nd	>5.5	○	○	●	○	●	○	○	●
Kuppens[50]	2010	Netherlands	108	Prospective	1st	>2.5	○	○	○	○	○	○	○	○
Männistö[52]	2010	Finland	224	Prospective	1st	>3.6	○	○	○	●	●	○	●	○
Negro[51]	2010	Italy	642	Prospective	1st	2.5-5.0	●	○	●	○	○	○	○	○
Goel[54]	2011	India	34	Prospective	All 3	>5.0	○	○	●	○	●	●	●	○
Su[55]	2011	China	41	Prospective	1st and 2nd	>4.3	●	●	●	○	○	○	○	○
Wilson[56]	2012	US	528	Prospective	1st and 2nd	>4.1	○	○	○	○	●	●	○	○
Tudela[57]	2012	US	528	Prospective	1st and 2nd	>4.1	○	○	○	●	○	○	○	○
Schneuer[58]	2012	Australia	152	Retrospective	1st	>2.9	●	●	●	○	○	●	○	○
Karakosta[59]	2012	Greece	79	Prospective	1st and 2nd	2.5 and 2.7	○	○	●	●	○	○	○	●
Korevaar[60]	2013	Netherlands	188	Prospective	1st and 2nd	4.04	○	○	●	○	○	○	○	○

● = Significant association found.
● = No significant association found.
○ = Association between thyroid disease and complication not evaluated.
SCH = Thyrotropin concentration (mIU/L).

Fig 1 | Data from 16 studies that have evaluated an association between thyroid disease and pregnancy and maternal, fetal, neonatal, or offspring complications. SCH=subclinical hypothyroidism

probably mildly iodine deficient.[45] The Institute of Medicine recommends a dietary intake of 220 µg iodine per day during pregnancy and 290 µg per day in breastfeeding women.[46] Consequently, many organizations, including the ATA, the ES, the AACE, and the Teratology Society recommend that all pregnant and breastfeeding women take a prenatal vitamin that contains 150 µg of potassium iodide.[47]

Impact of subclinical hypothyroidism on pregnancy outcome and intellectual development of the fetus

Studies have evaluated the impact of hypothyroidism on the outcome of pregnancy for more than 50 years, and early studies provided clear evidence of a link between overt hypothyroidism and adverse events.[48] Subsequent studies have confirmed that gestational hypertension, pre-eclampsia, increased placental weight, cretinism, low birth weight, fetal death, spontaneous abortion, and intrauterine growth retardation are all associated with overt hypothyroidism in pregnancy.[49] Therefore, it is now well accepted that the detection and treatment of pregnant women with overt hypothyroidism is crucial to both maternal and fetal health.

Pregnancy complications excluding neuro-intellectual development

To date, 16 observational studies have evaluated the association between subclinical hypothyroidism and complications of pregnancy that are not related to the neuro-intellectual development of the offspring. Figure 1 presents the 16 studies, all of which have been published in the past 20 years.[27 30 34 36 39 50-60]

In these mostly prospective observational studies, the cut off used to define subclinical hypothyroidism and the point in gestation at which thyrotropin was assessed varied. Some evaluated fewer than 100 women with subclinical hypothyroidism and are therefore underpowered to detect the pregnancy and neonatal complications studied, which occur in a small proportion of pregnant women. Preterm delivery, miscarriage, and gestational hypertension were associated with subclinical hypothyroidism in two or more studies.

Eight further studies focused on evaluating the rate of subclinical hypothyroidism in a population of women with specific pregnancy related complications. Four studies focused on preterm delivery. One found a threefold increase in subclinical hypothyroidism (thyrotropin ≥3.0 mIU/L) in women with very preterm delivery (n=28) compared with 124 women who delivered at term.[61] However, the other three studies did not report an increased prevalence of subclinical hypothyroidism in women who delivered preterm compared with those who delivered at term.[62-64]

A Dutch study found a significant increase in the rate of subclinical hypothyroidism (thyrotropin ≥2.5 mIU/L) in 58 women who presented in the breech position compared with 1000 women who presented in the cephalic position.[51] Another study found that, in the third trimester of pregnancy, thyrotropin concentrations were significantly

higher in 100 women with pre-eclampsia than in 50 gestation matched normotensive controls (thyrotropin 5.63 *v* 2.00 mIU/L).[65]

Only one randomized placebo controlled trial has assessed whether levothyroxine therapy would decrease the rate of adverse pregnancy and neonatal events in subclinical hypothyroidism.[66] It screened 4562 women at a mean gestational age of 8.8 weeks. Tests for thyrotropin, free thyroxine, and thyroid antibodies were performed immediately in half of the women and serum samples were frozen and assayed after delivery in the other half. Women treated during pregnancy had a significant decrease in the rate of adverse obstetrical and neonatal outcomes (number needed to treat 40, 95% confidence interval 1.4 to 2.5).

Neurologic and intellectual complications

Maternal thyroxine is crucial for the normal neurodevelopment of the fetus. Animal studies have shown that maternal hypothryroxinemia, with or without raised thyrotropin, can result in adverse neurodevelopmental outcomes.[67] Not surprisingly, therefore, in the past two decades most attention has been paid to the impact of maternal subclinical hypothyroidism on the intellectual and neurologic development of children.

The first study to confirm the association was published in 1999.[68] It compared the IQ of 64 children (age 7-9 years) born to mothers with thyrotropin values above the 98th centile with that of 124 children born to euthyroid pregnant control women. The mothers were part of a cohort of 25 216 women previously screened for Down's syndrome in the second trimester. Of the 64 women with raised TSH concentrations during pregnancy, 48 were not treated with levothyroxine. The IQ of the offspring of these 48 women was 7 points lower than that of the offspring of the 128 controls (P=0.005).

Subsequently, two smaller studies assessed the association between subclinical hypothyroidism and neurologic development of the newborn. One found a significant decrease in the mean mental developmental index (MDI) in the offspring of seven women with subclinical hypothyroidism during pregnancy compared with that of the offspring of six women who were euthyroid during pregnancy.[69] The other screened 1268 women at gestational weeks 16-20 for thyroid function and assessed the intellectual and motor development of their children at the age of 25-30 months.[70] Children of the nine mothers with subclinical hypothyroidism during pregnancy had significantly lower scores on the Bayley Scale of Infant Development and the MDI when compared with the offspring of mothers who were euthyroid during pregnancy.

In 2012, a prospective multi-country randomized controlled trial in Europe assessed the impact of levothyroxine in 21 846 women with a thyrotropin concentration greater than the 97.5th centile or free thyroxine lower than the 2.5 centile (or both).[71] Serum samples were obtained at a mean gestational age of 12 weeks and three days, and the primary outcome variable was the children's IQ at 3 years of age. Mean IQ and the proportion of children with IQ levels below 85 were not significantly different between the 390 children of the mothers treated during pregnancy and the 404 children of those who were not treated.

It is difficult to compare the results of the above studies because of differences in the patients' ages and the tests used. It is plausible, for example, that subclinical hypothyroidism, rather than reducing global IQ, may exert detrimental effects on specific functions, such as memory or visuospatial and orientation performance.

Studies that included women with subclinical hypothyroidism or overt hypothyriodism

Three other studies that assessed adverse outcomes in women with subclinical hypothyroidism or overt hypothyroidism are worth noting. The first was a retrospective electronic chart analysis of the US Cohort Consortium on Safe Labor data, which analyzed thyroid status and pregnancy outcome in 223 512 singleton pregnancies. Hypothyroidism (subclinical hypothyroidism was not differentiated from overt hypothyroidism) was significantly associated with pre-eclampsia, gestational diabetes, preterm birth, cesarean section, admission of the mother to intensive care, placental abruption, and breech position.[72]

The second study from the same US cohort found that maternal hypothyroidism increased the risk of neonatal sepsis, respiratory distress syndrome, transient tachypnea, and apnea.[73]

A study of 2497 Dutch women found a positive linear association between risk of child loss, and thyrotropin values, which extended into the normal range (for example, the absolute risk for child loss increased from 0.8% in women with a thyrotropin of 0.54 mIU/L to 2.2% when thyrotropin was 3.13 mIU/L).[74]

Finally, three further studies have evaluated pregnancy outcome in women being treated for hypothyroidism during pregnancy. A retrospective study of 150 women with hypothyroidism, 99 of whom were on treatment before conception, found that when treatment was inadequate (thyrotropin ≥4.0 mIU/L during pregnancy), 71% of the women with subclinical hypothyroidism aborted.[75] Another reported on pregnancy outcomes in 848 468 women included in the Swedish Health Register, 9866 of whom were on thyroid hormone.[76] Women treated with thyroid hormone had a significantly increased risk of congenital malformations, preterm birth, cesarean section, gestational diabetes, and pre-eclampsia. A study of 203 American women who had previously had subclinical hypothyroidism during pregnancy found increased rates of gestational diabetes and stillbirth in a subsequent pregnancy.[77]

Overall, evidence published over the past 20 years supports an association between subclinical hypothyroidism and adverse maternal, fetal, and neonatal outcomes. Although not all studies found such associations, many of the negative studies had inadequate study size and a lack of power to find any association that might exist. Alternatively, in some, screening was performed too late in pregnancy. However, some well designed studies have found no link between subclinical hypothyroidism and adverse pregnancy outcomes.

Results from studies of association should always be interpreted with caution, and this is especially so for studies of thyroid function in pregnancy. This is because hypothyroidism may worsen in women with subclinical hypothyroidism in the first trimester as pregnancy progresses—this

is particularly true for those who are TPO-Ab positive. Conversely, some women, particularly those who are TPO-Ab negative, return to the euthyroid state as pregnancy proceeds.[4 20] Ongoing prospective studies will be invaluable in further defining the association between subclinical hypothyroidism and maternal, fetal, and neonatal outcomes.

Treatment of subclinical hypothyroidism

The decision on whether to treat subclinical hypothyroidism diagnosed during pregnancy is controversial. The ATA 2011 and the ES 2012 guidelines, but not the American College of Obstetricians and Gynecologists guidelines, recommend initiating levothyroxine therapy in these patients.[8 9 78] For physicians who elect to start treatment, the evidence on the timing and dose modification is presented below.

Women without pre-existing hypothyroidism

Evidence on the appropriate dose of levothyroxine in pregnant women newly diagnosed with subclinical hypothyroidism is limited. A prospective randomized controlled trial gave all women 150 µg of levothyroxine from the start of treatment.[71] A high dose was used because of the need to normalize maternal thyrotropin and free thyroxine values rapidly. In 85% of women, the dose did not need to be modified during pregnancy, whereas 10% needed a decrease in dose to 125 µg and 5% required an increase to 175 µg.

In another prospective trial of levothyroxine in 56 women with subclinical hypothyroidism first diagnosed during pregnancy,[79] the starting dose of levothyroxine was based on the initial thyrotropin value. Women whose thyrotropin was 2.5-5.0 mIL/U were started on 50 µg per day, women with a thyrotropin of 5.0-8.0 mIU/L were started on 75 µg per day, and those with thyrotropin greater than 8.0 mIU/L were given 100 µg per day. Over 80% of the women did not require any dose adjustment during pregnancy.

A retrospective study assessed 64 women with new onset subclinical hypothyroidism during pregnancy.[80] The goal of treatment was to achieve a thyrotropin of 2.5 mIU/L or less in the first trimester and 3.0 mIU/L or less in the second and third trimesters. Women with a presenting thyrotropin of 2.5-4.2 mIU/L needed 1.20 (standard deviation 0.39) µg per kg per day (mean dose 77.98 µg/day) of levothyroxine, whereas those with a presenting thyrotropin of 4.2-10.0 mIU/L needed 1.42 (0.31) µg per kg per day (95.35 µg/day). In 89% of the women the initial dose of levothyroxine did not need to be modified as pregnancy progressed.

Women with pre-existing hypothyroidism

Women with pre-existing hypothyroidism often need a higher dose of levothyroxine during pregnancy to maintain euthyroidism. Several studies have investigated this important issue, and their main results are summarized in chronological order. A retrospective analysis of thyroid function and levothyroxine dose requirements in 12 women found that all had a rise in thyrotropin during pregnancy and 75% needed an increase in levothyroxine dose of about 50 µg per day.[81] Postpartum, the mean thyrotropin value in all women decreased, indicating a decline in the post-pregnancy thyroxine dose requirement.

A prospective study found that the dose of levothyroxine needed to be increased in 17 of 20 women who became pregnant. The increase was seen as early as the fifth gestational week and the average increment was 47%.[82]

The thyrotropin concentration before pregnancy affects if, and how much, levothyroxine will need to be increased during pregnancy. A prospective study found that before pregnancy the mean thyrotropin value was lower in 50 women who did not need additional levothyroxine during pregnancy than in the 34 women who needed an increase (1.36 *v* 4.63 mIU/L).[83] Similarly, a prospective study found that only 17% of women with a thyrotropin less than 1.2 mIU/L before conception needed an increase in their dose during pregnancy compared with 50% of women whose preconception thyrotropin was 1.2-2.4 mIU/L.[84]

A randomized trial compared two different levothyroxine regimens during pregnancy in women with pre-existing hypothyroidism.[85] The daily prepregnancy levothyroxine dose was increased by two tablets a week in one group and by three tablets a week in the second group. Thyroid function tests were performed every two weeks during pregnancy. Increasing the pregestation dose, by either two or three tablets, maintained thyrotropin below 5.0 mIU/L in all women. Thyrotropin was below 0.1 mIU/L in only 8% of women on the two extra dose regimen, whereas suppression of thyrotropin was found in 26% of women who took three extra tablets. Most (92%) abnormal thyrotropin values were detected by monitoring thyroid levels every four weeks.

Maintenance and monitoring of levothyroxine therapy

During pregnancy the thyroid gland must produce 30-50% more thyroxine to maintain the euthyroid state. This results in new onset subclinical hypothyroidism in women who were euthyroid before pregnancy but had decreased thyroidal reserve (most often as a result of autoimmune thyroid disease). Whether levothyroxine therapy should be continued postpartum, when increased thyroid hormone production is no longer necessary, is an important question. A recent retrospective study followed up 65 women who developed subclinical hypothyroidism during pregnancy but stopped taking levothyroxine postpartum.[86] Most women (75%) were euthyroid after five years, whereas 25% had a persistently raised thyrotropin (>4.5 mIU/L). The presence of TPO-Ab was the most important risk factor for a raised thyrotropin.

Recommendations

Both the ATA 2011 and the ES 2012 guidelines contain recommendations for the initiation of levothyroxine for subclinical hypothyroidism during pregnancy and the frequency of thyrotropin monitoring once treatment is started.[8 9] The ATA guidelines recommend that all pregnant women with thyrotropin greater than 2.5 mIU/L and normal free thyroxine who are TPO-Ab positive and all women with thyrotropin greater than 10.0 mIU/L, irrespective of the free thyroxine value, be treated with levothyroxine. The guidelines concluded that insufficient data were available for TPO-Ab negative pregnant women with a thyrotropin greater than 2.5 mIU/L.

The ES guidelines recommend that all women with a thyrotropin greater than 2.5 mIU/L and normal free thyroxine in the first trimester be treated with levothyroxine, irrespective of their TPO-Ab status. The ES guidelines recommend that thyrotropin testing is repeated every four to six weeks

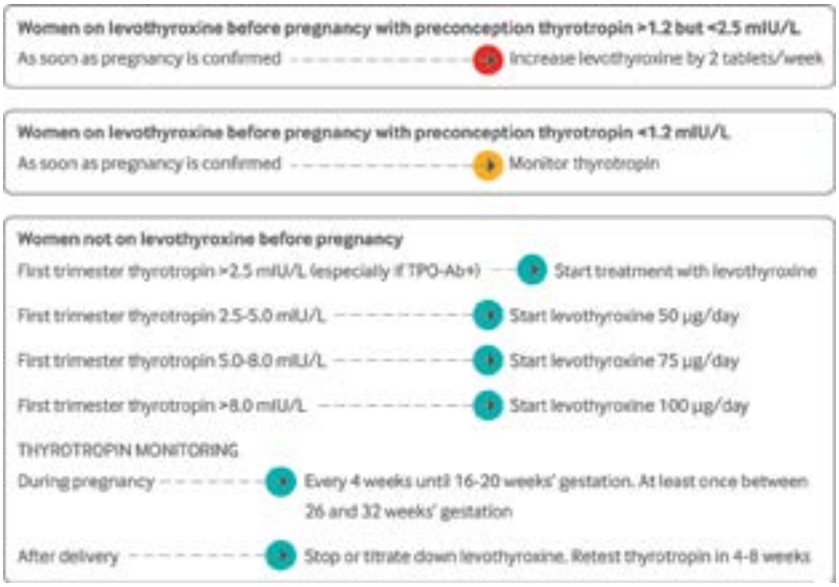

Fig 2| Treatment algorithm for women taking levothyroxine before pregnancy.[78] TPO-Ab=anti-thyroid peroxidase antibodies

throughout pregnancy and the ATA guidelines recommend testing every four weeks until 16-20 weeks and at least once between 26 and 32 weeks' gestation.

In 2013, clinical members of the ES, the ATA, and the AACE were asked to fill in a web based survey consisting of 30 questions that dealt with testing, treatment, and modulating factors in the management of primary hypothyroidism. Results showed that 96.1% of respondents used a thyrotropin target of less than 2.5 mIU/L in newly pregnant women, whereas 63.5% preferred a target of less than 1.5 mIU/L. In addition, 67.7% would check thyroid hormone concentrations every four weeks during pregnancy, and 21.4% would check every eight weeks. Only 36.9% of respondents said they would immediately increase the dose of levothyroxine in a hypothyroid patient with a thyrotropin of 0.5 mIU/L who became pregnant.[87]

Application in clinical practice

Although the results of the survey demonstrate good adherence to current guidelines, in clinical practice pregnant women on thyroxine substitution are often dysregulated—about 50% of women have a raised thyrotropin concentration in the first half of gestation.[88 89]

Subclinical hypothyroidism has been associated with multiple adverse maternal, fetal, and neonatal outcomes, and a preliminary intervention trial suggests that treatment is beneficial.[66] On the basis of current evidence, we believe it is reasonable to recommend treating women with new onset subclinical hypothyroidism during pregnancy. Levothyroxine therapy during pregnancy is inexpensive and has been shown to be safe.

We recommend adoption of the treatment algorithm recommended by Yu and colleagues, which is based on the initial maternal thyrotropin value.[79] Those with a thyrotropin value of 2.5-5.0 mIU/L, 5.0-8.0 mIU/L, and greater than 8.0 mIU/L should be started on levothyroxine at 50 µg, 75 µg, and 100 µg per day, respectively. After delivery levothyroxine can be stopped or titrated down and retested in four to eight weeks in women who are not planning on having more children. It is recommended that women who are planning on pregnancy within the next couple of years carry on taking levothyroxine to ensure that they are euthyroid at the time of conception.

Women on levothyroxine before pregnancy with a thyrotropin value less than 1.2 mIU/L may not need an increase in levothyroxine but require ongoing monitoring. Irrespective of the prepregnancy thyrotropin value, all patients should be instructed to have thyrotropin measured as soon as pregnancy is confirmed. Figure 2 summarizes these recommendations.

Screening for thyroid disease in pregnancy

Debate about the need for universal screening for thyroid dysfunction during pregnancy is ongoing. The expert panel involved in producing the ES guidelines on thyroid and pregnancy could not reach consensus—some participants concluded that universal screening is warranted, whereas others thought that a case finding strategy should be initiated.[9]

Guidelines from AACE, the Society of Maternal-Fetal Medicine, the American College of Obstetrics and Gynecology, the Cochrane Collaboration, and the ATA all endorse a case finding strategy.[8 78 90-92] Those who favor universal screening cite the increased prevalence of hypothyroidism (overt and subclinical) during pregnancy, the inexpensive nature of the treatment (levothyroxine), the wide availability of an inexpensive screening test (thyrotropin measurement), and the cost effectiveness of a screening strategy. Those who oppose universal screening cite the paucity of evidence that identification and treatment of pregnant women with subclinical hypothyroidism improves maternal or neonatal outcomes.

The main unresolved point in the debate about universal screening is the lack of an agreed policy on whom to treat given the paucity of randomised controlled trials in pregnant women with subclinical hypothyroidism. As discussed earlier, many studies and meta-analyses have documented an association between subclinical hypothyroidism and gestational diabetes, miscarriage, preterm delivery, gestational hypertension, pre-eclampsia, and impaired neuropsychological development of the offspring. However, only two randomised controlled trials have been published that have investigated the potential benefits of treating maternal subclinical hypothyroidism.

Case finding as a strategy for identifying women with thyroid disease during pregnancy has limitations. Firstly, data from prospective studies have shown that when risk factors for thyroid disease are used, case finding will miss between 33% and 81% of pregnant women with hypothyroidism.[67 93-95] Secondly, a large number of risk factors need to be evaluated, which is time consuming. Thirdly, obstetricians and gynecologists provide the majority of pregnancy related care. Studies have reported that some obstetricians have limited knowledge about the association between thyroid disease and pregnancy.[96 97]

Even the risk factors that need to be included in a case finding strategy are controversial. Both the ATA 2011 and ES 2012 guidelines recommend screening all women over the age of 30 years. Although one analysis found no significant association between age and abnormal thy-

FUTURE RESEARCH QUESTIONS

Is there a thyrotropin threshold above which the rate of adverse obstetrical or fetal events is substantially increased?

Does the treatment of subclinical hypothyroidism during pregnancy decrease the risk of adverse events in the mother and the fetus?

Does the treatment of hypothyroxinemia during pregnancy decrease the risk of adverse events in the mother and the fetus?

Does maternal subclinical hypothyroidism cause a decrease in the IQ of the offspring?

rotropin values, in a subgroup analysis of risk factors for hypothyroidism, the addition of women aged 30 years or more increased the proportion of women identified in a case finding screening strategy from 55.3% to 85.6%.[98]

Geographic considerations

The thyrotropin concentration at which women should be diagnosed with subclinical hypothyroidism varies by region. As noted earlier, it is recommended that local guidelines be developed to determine the normal thyrotropin range for the three trimesters of pregnancy.[8 9] Consequently, a patient with a thyrotropin of 4.0mIU/L would be diagnosed with subclinical hypothyroidism in the US but not in China or India.[20 21] This may prove confusing to physicians and patients. Furthermore, it is unclear whether the thyrotropin value above which the incidence of a particular complication increases is the same as for other complications.

Finally, geographic differences in clinical practice affect the care that a patient receives. A 2010 survey of members of the European Thyroid Association reported a wide variation in clinical practice regarding the diagnosis and treatment of thyroid disease in pregnancy. The survey found that 42% of responders, or their institutions, screened all pregnant women for thyroid dysfunction, 43% performed targeted screening of only high risk women, whereas 17% carried out no systematic screening. Timing of the screening, tests used, and criteria for starting treatment and monitoring varied.[99] In the US the approach to screening also varies widely. A study from Boston Medical Center showed a screening rate of 85%, whereas another national study in the US reported a screening rate of only 23%.[37 100]

Current evidence on subclinical hypothyroidism does not support universal screening. However, the incidence and impact of overt hypothyroidism and the ability of treatment to prevent associated adverse events is sufficient to justify universal screening for thyroid disease.[48 101 102] In support of this position, a cost effective analysis showed that universal screening with the goal of identifying and treating overt hypothyroidism is cost effective.[103] Because universal screening would also identify patients with subclinical hypothyroidism, these patients should be treated as indicated in current guidelines unless ongoing and future studies prove otherwise.

Future studies

Three ongoing randomized prospective trials will yield important data that should be instrumental in informing future guidelines on thyroid and pregnancy. A National Institute of Child Health and Human Development study is screening pregnant women of less than 20 weeks' gestation for subclinical hypothyroidism or hypothyroxinemia. Women will be randomized to treatment with levothyroxine or placebo until delivery (http://clinicaltrials.gov/ct2/show/NCT00388297). The offspring will have annual developmental testing until age 5 years to determine whether treatment improves IQ.

In the United Kingdom, the Thyroid AntiBodies and LEvoThyroxine (TABLET) trial is recruiting euthyroid TPO-Ab positive women before conception and treating half with levothyroxine and half with placebo (www.controlled-trials.com/ISRCTN15948785). The major outcome variables are the rate of miscarriage and preterm delivery.

Finally, in China 4800 women have been enrolled in the Subclinical Hypothyroid and Iodine Deficiency in Early Pregnancy and Women Planning for Pregnancy: Screening and Intervention (SHEP) trial. A major factor being assessed is the impact of levothyroxine on fetal brain development.[104]

Conclusion

The past two decades have seen major advances in our understanding of the physiological changes that occur in the thyroid during pregnancy and the impact of subclinical hypothyroidism on adverse maternal and fetal outcomes. The normal upper range of thyrotropin is 2.5 mIU/L in the first trimester of pregnancy and 3.0 mIU/L in the second and third trimesters. Hypothyroidism is present in 2-15% of pregnant women. It is mainly caused by iodine deficiency in developing countries and autoimmune thyroid disease in developed countries. Subclinical hypothyroidism has been associated with multiple negative outcomes, including pregnancy loss, preterm delivery, gestational diabetes, and impaired neurologic development in the offspring. Women on levothyroxine before conception require careful management to ensure that the euthyroid state is maintained throughout pregnancy.

Although it is well accepted that treating overt hypothyroidism decreases maternal and fetal adverse outcomes, current data on the impact of treating subclinical hypothyroidism are limited and conflicting. Universal screening of all pregnant women to detect and treat overt hypothyroidism is recommended. Ongoing prospective trials will provide future guidance on the efficacy of treating subclinical hypothyroidism during pregnancy.

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