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**REVIEW**

- 1 Hypothyroidism during pregnancy: Controversy over screening and intervention

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## Hypothyroidism during pregnancy: Controversy over screening and intervention

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### Abstract

Thyroid hormones are critical for foetal neurological development and maternal health. Maternal hypothyroidism during pregnancy is associated with adverse impact on health of the mother as well as the progeny. Reduced thyroid hormone levels predispose the child to develop mental retardation and cognitive delay in early life. In the mother, hypothyroidism during pregnancy is associated with spontaneous abortion, placental abruption, preterm delivery and hypertensive disorders. Therefore, screening and therapeutic intervention is justified to prevent foetal as well as maternal co-morbidities. In view of impact of such a large-scale screening and intervention program on limited healthcare resources, it is debatable if a targeted rather than universal screening program will result in comparable outcomes. In addition, there is an ongoing debate regarding best evidence-based practice for the management of isolated hypothyroxinaemia, subclinical hypothyroidism and euthyroid women with autoimmune hypothyroidism. We have carried out a review of the literature; firstly, to determine whether universal screening for asymptomatic women in early pregnancy would be cost-effective. Secondly, we have retrospectively reviewed the literature to analyse the evidence regarding the impact of therapeutic intervention in women with subclinical hypothyroidism.

**Key words:** Targeted screening; Thyroid peroxidase antibodies; Isolated hypothyroxinaemia; Spontaneous abortion; Overt hypothyroidism; Placental abruption; Universal screening; Hypothyroidism during pregnancy; Subclinical hypothyroidism; Autoimmune hypothyroidism

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**Core tip:** Hypothyroidism during pregnancy poses a significant health challenge as it is associated with adverse health outcomes for mother as well as the child.

There is evidence that supports increased maternal and neonatal morbidity, even in absence of a clinically overt maternal hypothyroid state. However, in view of limited available healthcare resources, the jury is still divided regarding use of universal *vs* targeted screening programs in pregnant women. In addition, there is a lack of consensus regarding the best management approach for isolated hypothyroxinaemia and subclinical hypothyroidism. Keeping these contentious issues in mind, we have carried out a review of the literature.

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## INTRODUCTION

Pregnancy is a physiological state of complex metabolic stress that involves significant changes in hormonal milieu. It has a profound influence on thyroid gland structure as well as function. Hypothyroidism during pregnancy constitutes a significant health challenge, as it is associated with adverse maternal outcome along with an impact on neonatal cognitive development. The foetal thyroid gland starts to function only after 12-14 wk of gestation. As a consequence, the growing foetus remains dependent upon maternal thyroid hormones during this phase of early gestation<sup>[1,2]</sup>. Thyroid hormones (thyroxine and triiodothyronine) are vital for normal foetal neurological development<sup>[3,4]</sup>, and decreased levels predispose the child to develop cognitive delay in early adolescence<sup>[5]</sup>. There are studies linking untreated maternal overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) with increased adverse maternal and foetal outcomes<sup>[6-8]</sup>, although, Cleary-Goldman *et al*<sup>[9]</sup> failed to demonstrate such an association with SCH. In a study carried out by Haddow *et al*<sup>[10]</sup>, children born to pregnant women with hypothyroidism had lower intelligence quotient (IQ) scores compared with children born to pregnant women without hypothyroidism. In addition, hypothyroidism during pregnancy has also been linked with spontaneous abortion, placental abruption, preterm delivery and hypertensive disorders<sup>[6,7,11,12]</sup>. Decreased IQ in children born to mothers with isolated hypothyroxinaemia (IH) has also been reported by Pop *et al*<sup>[13]</sup> and Li *et al*<sup>[14]</sup> and further supported by Henrichs *et al*<sup>[5]</sup> in the largest prospective Generation R study. Even in euthyroid women with high titre thyroid peroxidase (TPO) antibodies, there is increased risk of adverse outcomes, such as foetal loss<sup>[15]</sup> and pregnancy-induced hypertension<sup>[16]</sup>. For these reasons, it is important to adopt appropriate strategies to identify women at these adverse outcomes and to implement screening tools for early detection and initiation of effective treatment.

However, there is an ongoing debate regarding cost-effectiveness of universal *vs* targeted screening in pregnant women<sup>[17,18]</sup>. In addition, there is a lack of consensus regarding the best evidence based approach for the management of isolated hypothyroxinaemia, SCH with or without TPO antibodies and euthyroid women with high TPO antibodies<sup>[15,19,20]</sup>. We have carried out a review of the literature; firstly, to determine whether universal screening for asymptomatic women in early pregnancy would be cost-effective. Secondly, we have retrospectively reviewed the literature to analyse the evidence regarding the impact of therapeutic intervention in women with subclinical hypothyroidism.

## Physiological changes in thyroid gland during pregnancy

Pregnancy has an intense influence on the thyroid gland and provokes several changes and metabolic effects that alter thyroid function. During the first stages of gestation, there is a rise in renal blood flow and glomerular filtration rate that results in more iodide disposal and reduced iodine blood level, an effect that persists until term. Further reduction of available iodine occurs later at 12-14 wk gestation, with more transfer of iodine from the mother to the foetal circulation at the time when the foetal thyroid gland starts to function. This reduction in maternal iodine level obliges a compensatory rise in iodide entrapment into the gland and increased thyroid activity. In women with satisfactory iodine reserve, there is mild thyroid burden. However, in geographical areas where the iodine resources are poor, the iodine losses in the urine and in placental transfer could constitute a significant issue<sup>[21]</sup>.

The structural similarity between human chorionic gonadotropin (hCG) molecule and thyroid stimulating hormone (TSH) renders the hCG molecule to behave as a weak thyrotropic hormone and may even enhance growth of the thyroid gland<sup>[22]</sup>. During the hCG peak at around the end of the first trimester, hCG stimulates thyroidal cells to secrete free thyroxin (FT<sub>4</sub>), and a temporary mild fall in basal TSH occurs<sup>[23]</sup>.

Thyroxine-binding globulin (TBG) is a carrier protein that binds thyroid hormones in serum. It has the highest binding affinity compared to other carrier proteins despite its lowest serum level. A significant elevation of serum TBG level has been shown in women during pregnancy due in part to oestrogen stimulation and decreased clearance<sup>[23]</sup>. Accordingly, thyroid gland production of FT<sub>4</sub> and FT<sub>3</sub> must increase to maintain adequate levels of thyroid hormone during pregnancy.

Moreover, the placenta plays a role in the metabolism of maternal thyroid hormones. Increased deiodination activity in the placenta might play a vital role in the passage of maternal thyroid hormones to the foetus<sup>[21]</sup>. The placenta synthesizes iodothyronine deiodinases type II (DIO2), which converts T<sub>4</sub> to T<sub>3</sub> through outer ring deiodination, and type III (DIO3), which deactivates

both T<sub>4</sub> and T<sub>3</sub> via inner ring deiodination. ID3 is the major deiodinase synthesized by the placenta and has significant deiodination activity<sup>[24]</sup>. In pregnant women treated for hypothyroidism, LT<sub>4</sub> should be increased to maintain euthyroidism in later stages of pregnancy<sup>[23]</sup>.

### **Effect of iron deficiency anaemia on thyroid status during pregnancy**

Worldwide, iron deficiency is the most common cause of anaemia during pregnancy, affecting around 50% of the pregnant population<sup>[25]</sup>. Several studies in animals and humans have suggested a link between iron deficiency anaemia and thyroid status. Thyroid peroxidase is the key enzyme in thyroid hormone synthesis. It has been shown by Hess *et al*<sup>[26]</sup> that the activity of this enzyme is impaired and the FT<sub>4</sub> and FT<sub>3</sub> levels are significantly reduced in rats with iron deficiency anaemia. In addition, Beard *et al*<sup>[27]</sup> showed a significant reduction in hepatic thyroxine-5'-deiodinase activity and FT<sub>3</sub> production in rats with iron deficiency compared with controls. In humans, previous studies showed reduced FT<sub>4</sub> and FT<sub>3</sub> levels in women with iron deficiency<sup>[28,29]</sup>. Recently, in an observational study Li *et al*<sup>[30]</sup> reported a significantly higher TSH and lower FT<sub>4</sub> during the first trimester in women with iron deficiency anaemia. They also observed a significantly higher rate of TPO antibodies in women with iron deficiency anaemia compared with control. It is worthwhile to note that the state of hypothyroidism in itself also can produce anaemia<sup>[31]</sup>; and, therefore, future research on this topic should aim to address this point.

### **Mechanism of implication of hypothyroidism in maternal and foetal consequences**

The risk of adverse consequences in pregnant women with hypothyroidism depends on the severity and sub-type of maternal hypothyroidism. Thyroid hormones are essential for regulation of metabolic activities in the brain, white fat, brown fat, skeletal muscle, liver and pancreas as well as regulation of growth development<sup>[32]</sup>. The molecular means by which thyroid hormones alter foetal neurological development remains unclear. However, experimental trials in animals showed delayed maturation of major structures, such as the cerebellum, in which there is interference of Purkinje cell maturation and delayed granular cell migration<sup>[33]</sup>. In addition, it has been reported that locally converted FT<sub>3</sub> in the brain from maternal FT<sub>4</sub> is critical for foetal brain development<sup>[34]</sup>. However, in animal studies, replacement with FT<sub>3</sub> does not offer adequate brain protection, indicating that normal maternal FT<sub>4</sub> level during early embryonic life is essential for brain development<sup>[35]</sup>.

The pathogenesis of maternal consequences is also complex and less understood. The mechanisms for infertility and miscarriage may involve the presence of thyroid auto-antibodies. Vitamin D deficiency may also contribute to autoimmunity and was shown to be reduced in patients with autoimmune thyroiditis<sup>[36]</sup>. In addition, a disturbance in folliculogenesis, fertilization

and embryogenesis was reported associated with the presence of TPO antibodies<sup>[21]</sup>. Dyslipidaemia associated with hypothyroidism and pregnancy, such as hypertriglyceridaemia, could explain the occurrence of hypertensive disorders<sup>[37]</sup>.

### **Epidemiology and classification of hypothyroidism during pregnancy**

The prevalence of hypothyroidism during pregnancy is variable, and this variability is mostly attributed to differences in geographical areas, analytical measurement and trimester-specific TSH limits used in diagnosis<sup>[38]</sup>. In general the prevalence rates were estimated to be 0.25%-2.5% for SCH, 0.2%-0.3% for OH<sup>[39]</sup> and 5%-15% for euthyroidism with autoimmune disease<sup>[40]</sup>.

Classification of hypothyroidism recognised during pregnancy is essential for epidemiological as well as clinical reasons. The American Thyroid Association (ATA) has defined hypothyroidism during pregnancy as the state of increased TSH level when other rare causes, such as TSH-secreting pituitary tumor and thyroid hormone, resistance are excluded. Primary maternal hypothyroidism (MH) observed during pregnancy should be distinguished from preexisting hypothyroidism diagnosed prior to the pregnancy. Two main varieties of primary MH are recognised by the ATA: overt hypothyroidism (OH) and subclinical hypothyroidism (SCH) based on the presence of elevated TSH and whether FT<sub>4</sub> level is decreased or within normal range. However, cases of isolated hypothyroxinaemia (IH) with normal TSH have also been recognised by the ATA as a third sub-type of MH<sup>[19]</sup>. In addition, women with increased TPO antibodies status and normal thyroid function have been observed to have an increased risk of developing SCH in early pregnancy, and this may also be recognized as a fourth sub-type of MH (Figure 1)<sup>[15]</sup>. The ATA defines OH as a TSH > 2.5 mIU/L and a lower serum FT<sub>4</sub> level or a TSH ≥ 10.0 mIU/L, regardless of FT<sub>4</sub> level. SCH is defined as a TSH between 2.5-10 mIU/L and a normal FT<sub>4</sub> level, and IH is defined as a TSH within normal limits together with lower FT<sub>4</sub> level<sup>[19]</sup>.

### **Interpretation of TFT during pregnancy**

Due to significant alterations in thyroid functions during pregnancy, levels of TSH and FT<sub>4</sub> should be interpreted using gestational age-specific reference ranges. Using these specific references, it would be possible to evaluate thyroid functions accurately and to help in defining thyroid disorders<sup>[41]</sup>. Consequently, the ATA<sup>[19]</sup> recommends that trimester-specific reference values of thyroid function test (TFT) should be applied during pregnancy. In view of an increased thyroxine-binding globulin (TBG) level and enhanced thyrotropic activity of hCG, women during pregnancy have decreased TSH levels (< 0.4 mIU/L) compared with preconception levels<sup>[19]</sup>. In addition, there is a significant reduction in serum FT<sub>4</sub> level observed with advancing pregnancy. Following delivery, restoration of TBG to preconception

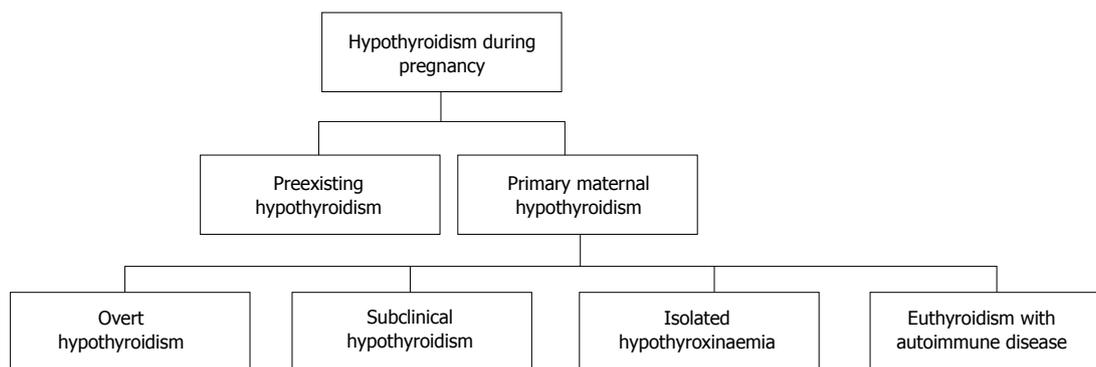


Figure 1 Classification of hypothyroidism during pregnancy<sup>[15,19]</sup>.

levels occurs within 4-6 wk together with FT<sub>4</sub> and FT<sub>3</sub> levels<sup>[42]</sup>. Several studies demonstrated that both reference limits for TSH were reduced during pregnancy, with the greatest reduction being noted during the first trimester when the thyrotropic effect of hCG was highest<sup>[41,43-45]</sup>. Panesar *et al*<sup>[43]</sup> showed increasing median TSH concentration throughout pregnancy: 0.80 (0.03-2.30) in the first trimester, 1.10 (0.03-3.10) in the second trimester and 1.30 (0.13-3.50) in the third trimester. Accordingly, in 2011, the ATA recommended TSH reference limits for each gestational age provided unavailability of specific ranges in the laboratory: 0.1-2.5 mIU/L for the first trimester, 0.2-3.0 mIU/L for the second trimester and 0.3-3.0 mIU/L for the third trimester<sup>[19]</sup>. On the other hand, accurate measurement of FT<sub>4</sub> concentration during pregnancy depends on the analytical technique used. Automated immunoassays (IAS) of FT<sub>4</sub> concentration are affected by elevated TBG, free fatty acids and reduced albumin levels, resulting in its unreliability<sup>[46-48]</sup>. The solid phase extraction-liquid chromatography/tandem mass spectrometry (LC/MS/MS) technique to estimate the level of FT<sub>4</sub> in the dialysate serum was proved highly specific as compared to the IAS method<sup>[49]</sup>. However, at present, the LC/MS/MS technique is not extensively used due to increased cost. According to Yue *et al*<sup>[48]</sup>, the reference ranges for FT<sub>4</sub> using the LC/MS/MS technique were found to decrease gradually with progression of pregnancy. In the 14<sup>th</sup> week gestation, the reference range was estimated between 1.08-1.82 ng/dL and decreased to 0.86-1.53 ng/dL by the end of 20<sup>th</sup> week gestation. Using the new technique, Kahric-Janjic *et al*<sup>[49]</sup> were able to show decreasing concentrations of FT<sub>4</sub> levels with progress in pregnancy (Figure 2), and the same results were obtained upon using IAS method on the same samples (Figure 3). The ATA recommends the LC/MS/MS technique as the ideal method to estimate FT<sub>4</sub> concentration during pregnancy. However, the ATA also recommends use of IAS methods with consideration of their limitations if LC/MS/MS technique is not attainable, and obviously, TSH measurement is a better estimate of TFT during pregnancy<sup>[19]</sup>.

## METHODOLOGY

### Data search

An extensive literature search of multiple data sources was performed in Pubmed, Cochrane library, Google Scholar and South Wales University Library (FINDit) up to December 20, 2016 for articles published in the English language. The keywords used to search in the data sources were: "thyroid function during pregnancy"; "hypothyroidism in pregnancy"; "thyroid dysfunction in pregnancy"; "outcomes and hypothyroidism in pregnancy"; "screening for hypothyroidism in pregnancy"; "interventions for hypothyroidism in pregnancy" and "treatment of hypothyroidism in pregnancy". All study types were selected for review, including experimental and observational trials (cohort and case-control), systematic reviews, meta-analyses, review articles and clinical guidelines. In addition, some references cited in the selected publications were also reviewed to analyse additional data.

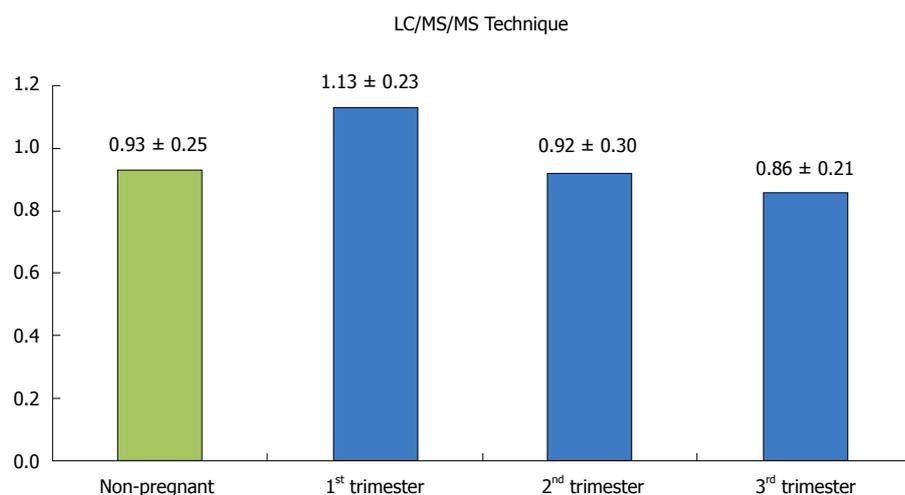
### Hypotheses

After reviewing the relevant literature, two hypotheses were postulated: Hypothesis-1, universal screening for asymptomatic women in early pregnancy will be effective; Hypothesis-2, therapeutic intervention in pregnant women with SCH and IH and euthyroid women with autoimmune hypothyroidism would be associated with reduced maternal and foetal adverse outcomes.

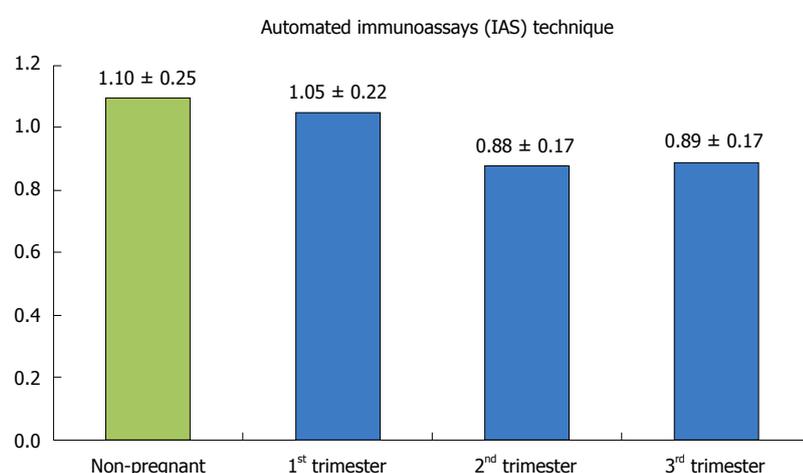
## SCREENING FOR HYPOTHYROIDISM DURING PREGNANCY

### Universal vs targeted screening

The observational studies by Haddow *et al*<sup>[10]</sup> and Pop *et al*<sup>[50]</sup> opened up the debate regarding cost-effectiveness of targeted vs universal screening in asymptomatic pregnant women for hypothyroidism. These studies observed an increased risk of neurological and cognitive development in children born to mothers with asymptomatic hypothyroidism. Several observational studies have focused on targeted screening by identifying



**Figure 2** Concentrations of serum free thyroxin (mean ± SE) using the solid phase extraction–liquid chromatography/tandem mass spectrometry (LC/MS/MS) technique in pregnant and non-pregnant women<sup>[49]</sup>.



**Figure 3** Concentrations of serum FT<sub>4</sub> (mean ± SE) using automated immunoassays technique in pregnant and non-pregnant women on the same samples<sup>[49]</sup>.

women as “high risk” to develop thyroid disease. These studies, however, have failed to spot more than 30% of pregnant women with SCH or OH<sup>[51,52]</sup>. On the other hand, prospective studies have shown no beneficial role of universal screening over selective approach or no screening in terms of improvement of adverse outcomes. For instance, Negro *et al*<sup>[8]</sup> randomised 4562 Caucasian women with no prior history of thyroid dysfunction into either universal or selective screening strategies and followed them prospectively. Women in both arms were classified on the basis of risk factors to develop thyroid dysfunction as “high risk” or “low risk”. Blood samples for FT<sub>4</sub>, TSH and TPO antibodies from all women in the universal screening strategy and “high risk” women in the selective screening arm were measured during the first trimester. In contrast, blood samples from “low risk” women in the selective screening arm were measured only during the post-partum period. Women with positive TPO antibodies and TSH more than 2.5 mIU/L received therapeutic intervention in the form of LT<sub>4</sub>. This study

showed that 1545 women in the selective screening arm and 1559 women in the universal screening strategy developed complications. However, the difference between the two groups was not statistically significant ( $P = 0.69$ ). Hypothyroidism developed in 1.9% of participants in the “low risk” selective arm who were only screened post-delivery, indicating that selective high-risk screening strategy missed a proportion of women with maternal hypothyroidism. Interestingly, “low risk” women in the universal screening arm who were identified to be hypothyroid and received LT<sub>4</sub> had fewer complications than “low risk” women in the selective screening arm. However, this difference was also statistically not significant. The strength of this study remains in its well-structured prospective design and randomization of various sub-groups, but its main drawback remains a homogeneous study population comprising of only Caucasian Italian women. As a result, the study results cannot be generalized to reflect accurately a wider heterogeneous and ethnically diverse population.

In another prospective study, Lazarus *et al*<sup>[53]</sup> tested 21846 pregnant women with no history of thyroid disease for TSH and FT<sub>4</sub> concentrations and then randomised them into either screening or control groups. In the screening, arm blood samples were analysed instantaneously at around the 13<sup>th</sup> week gestation; and in the control arm, samples were frozen and only tested post-delivery. Women with a TSH more than 97.5<sup>th</sup> percentile, FT<sub>4</sub> less than 2.5<sup>th</sup> percentile, or together were considered hypothyroid and were treated with 150 µg of LT<sub>4</sub>, with doses adjusted according to TSH concentrations (target TSH range 0.1-1.0 mIU/L). The IQ of children born to women with hypothyroidism was assessed at the age of 3-years by two psychologists. This study demonstrated that 12.1% of children in the screening strategy scored an IQ < 85 compared with 14.1% in the control arm. However, the difference was not statistically significant between the two groups ( $P = 0.39$ ), indicating that screening and treatment of hypothyroidism at around the 13<sup>th</sup> week gestation was not clinically beneficial in improving intellectual abilities in children at the age of 3-years. These results could be attributed to delayed gestational screening and a later initiation of LT<sub>4</sub> treatment, which might not have a significant effect on neurological development. Moreover, the IQ assessment of children at the age of 3-years could be too early to obtain an effect of LT<sub>4</sub> therapy, unlike in Haddow *et al*<sup>[53]</sup>, where children were assessed at the age of 7-years. The statistically insignificant difference obtained between the two groups could also be attributed to the risk of bias, as about 25% women were lost to follow-up.

Based on history taking, clinical examination and previous laboratory findings, the Endocrine Society recommends identifying a group of women as "high risk" to develop thyroid disease that should be targeted for selective screening (Table 1)<sup>[20]</sup>. One observational study that tested the efficacy of targeting "high risk" women in detection of thyroid abnormalities during pregnancy observed that women grouped as "high risk" have over six times increased risk to develop OH or SCH during pregnancy<sup>[52]</sup>.

#### **General criteria for justification of disease screening**

In general, screening is recommended to provide early detection of a particular condition among the apparently well asymptomatic individuals with the aim of reducing its burden in the community and consequently offering an opportunity to start specific an intervention at an earlier stage. Screening process should fulfill several criteria to be deemed appropriate as well as cost-effective. An effective screening program has significant influence on health care planning services. Historically, Wilson and Jungner, (1968) had set certain criteria that form the basis of the World Health Organization (WHO) to screen for a particular disease (Table 2)<sup>[54]</sup>. In view of the key role of screening in health care, it is important to examine the advantages of universal screening for hypothyroidism during pregnancy using the Wilson and

Jungner criteria.

#### **Is hypothyroidism during pregnancy an important health issue?**

Hypothyroidism during pregnancy is the second most common endocrine disorder, with only gestational diabetes mellitus (GDM) being more common<sup>[55,56]</sup>. The prevalence of hypothyroidism may even be higher if women with recently redefined trimester specific TSH values (TSH > 2.5 mIU/L) recommended by the ATA were included as a cut off for diagnosis of SCH. In addition, women with increased TPO antibodies and cases of isolated hypothyroxinaemia may be included in the spectrum of hypothyroidism<sup>[19]</sup>. In areas of iodine sufficiency, half of women with SCH have autoimmune hypothyroidism, as evidenced by positive TPO antibodies<sup>[57]</sup>. Recently, Blatt *et al*<sup>[17]</sup> extracted laboratory information for 502036 women during pregnancy from the Quest Diagnostics Informatics Data Warehouse. Of these women, 117892 underwent screening for OH and SCH by TSH measurement using trimester-specific reference limits. This study showed that 15.5% of women have OH or SCH, as evidenced by elevated TSH measurement, and the rate was 15.1% after adjustment for age. These results suggested that hypothyroidism during pregnancy could be even more widely prevalent than what is commonly accepted. Clearly, the epidemiological data supporting a relatively widespread prevalence of thyroid dysfunction in pregnant women justifies the need for universal screening.

#### **Evidence of associated adverse outcomes**

From a historical perspective, Man and Jones<sup>[58]</sup> reported compromised cognitive capabilities in children born to mothers with hypothyroidism. They included 1394 pregnant women into the study and measured their butanol extractable iodines to identify hypothyroid women along with assessment of mental and motor development in their children using Bayley's scales. Later, Matsuura and Konishi<sup>[3]</sup> also suggested that intellectual development is critically compromised in children born to mothers with hypothyroidism caused by Hashimoto's thyroiditis.

Recent studies have demonstrated conflicting results regarding the association of maternal hypothyroidism with cognitive impairment in the offspring. For instance, Haddow *et al*<sup>[10]</sup> in a large-scale prospective study observed an adverse impact on neuropsychological status of children born to mothers with undiagnosed hypothyroidism. The neuropsychological status in children of hypothyroid women and controls was recorded using the full-scale IQ scores (15 tests). An average of 4 points lower IQ scores was observed in children born to women with hypothyroidism who were treated as compared with the controls (children born to euthyroid women), although this reduction was deemed statistically no significant ( $P = 0.06$ ). However, a significant reduction in IQ scores, by an average of 7 points, was reported among untreated hypothyroid women compared with the controls ( $P =$

**Table 1 Risk factors for thyroid disease defined by the endocrine society<sup>[20]</sup>**

Women over the age of 30
Family history of autoimmune thyroid illness or hypofunction
Women with thyroid swelling
Women with thyroid antibodies (mainly TPO)
Symptoms or signs indicative of hypothyroidism
Women with T1DM, or with any autoimmune diseases
Women with previous history of abortion and premature birth
Women with history of previous head or neck radiation or thyroidectomy
Women on thyroid hormones replacement therapy
Women living in a geographical area lacking iodine

TPO: Thyroid peroxidase.

**Table 2 Wilson and Jungner criteria for disease screening<sup>[54]</sup>**

The condition sought should be an important health problem
There should be an accepted treatment for patients with recognised disease
Facilities for diagnosis and treatment should be available
There should be a latent or early symptomatic stage
There should be a suitable test or examination
The test should be acceptable to the population
The natural history of the condition should be adequately understood
There should be an agreed policy on who to treat as patients
The cost of case finding should be cost-effective
Case finding should be a continuing process and not a "once and for all" project

0.005). This study remained observational in design; and, therefore, it would be difficult to conclude about the efficacy of screening and treatment in neuropsychological achievement without adjustment of major confounders, such as direct measurement of parental IQ.

In contrast to observational studies, Lazarus *et al.*<sup>[53]</sup> showed in a prospective randomised trial that screening and treatment of hypothyroidism were not significantly beneficial in improvement of cognitive abilities in children born to mothers with hypothyroidism. However, this trial was criticised due to significant loss to follow-up (25% of women) and initiation of LT<sub>4</sub> therapy beyond a critical time that might have a significant influence on cognitive function. In addition, women included in this trial might have had milder hypothyroidism (mean TSH level 3.8 mIU/L)<sup>[53]</sup> than women in the Haddow trial (mean TSH level 13.2 mIU/L)<sup>[10]</sup>.

The association of maternal hypothyroidism with obstetric complications was also reported in several trials and results were also conflicting. For instance, Casey *et al.*<sup>[7]</sup> recruited pregnant women for measurement of TSH and FT<sub>4</sub> during routine antenatal care at around the 20<sup>th</sup> week gestation or less and followed them prospectively to assess for obstetric outcomes associated with SCH. In this study, 404 out of 17298 pregnant women were identified to have SCH, and they were found to have three-fold increased risk to develop abruptio placentae and two-fold risk of preterm delivery. In another study,

using data from prospective prenatal population-based study, Wilson *et al.*<sup>[59]</sup> found a significant association between SCH and risk of preeclampsia in pregnant women ( $P = 0.03$ ). Negro *et al.*<sup>[60]</sup> conducted a secondary analysis of the original prospective and randomised Negro *et al.*<sup>[8]</sup> that tested the influence of LT<sub>4</sub> therapy on adverse outcomes. Women with negative TPO antibodies were grouped into either TSH between 2.5-5.0 mIU/L or < 2.5 mIU/L. There was a significant difference in the rate of pregnancy loss between the two groups (6.1% in the group with higher TSH level vs 3.6% in the group with lower TSH level) ( $P = 0.006$ ).

On the contrary, Cleary-Goldman *et al.*<sup>[9]</sup> used stored blood samples from the prospective multicenter First And Second Trimester Evaluation of Risk (FASTER) to evaluate whether maternal hypothyroidism was associated with adverse obstetric outcomes. In the secondary analysis, SCH was observed in 2.2% of women and was not associated with an increased risk of obstetric complications, such as preterm labor, hypertensive disorders, preterm delivery and miscarriage. IH was observed in 2.3% of women and was associated with fewer obstetric complications (preterm labor, macrosomia in the first trimester and GDM in the second trimester). This study also demonstrated that both thyroglobulin autoantibodies (TGAb) and thyroid peroxidase (TPO) antibodies were associated with an increased risk of premature rupture of membranes<sup>[9]</sup>.

### Is universal screening cost effective?

Ideally, well-designed randomised controlled trials (RCTs) can provide evidence to ascertain benefits of universal screening over a selective "high risk" approach. However, even if such evidence was to show a clear advantage of universal screening and clinical benefits of initiating LT<sub>4</sub> therapy, it is not debatable if this approach would be preferable from a health-economic point of view. Danese *et al.*<sup>[61]</sup> conducted a cost-utility analysis of screening adults above 35 years old for thyroid dysfunction utilising costs in dollars and health benefits in quality adjusted life year (QALY) gained. They demonstrated that the cost-effectiveness of screening adults above 35 years old using measurement of TSH was \$9223/QALY, \$22595/QALY for women and men respectively and that the screening was markedly cost-effective in older women. Similarly, Bona *et al.*<sup>[62]</sup> showed that screening was cost-effective in adults above 60 years old.

Cost analyses evaluating screening for hypothyroidism in pregnant women have suggested cost-effectiveness of universal screening. Dosiou *et al.*<sup>[63]</sup> compared costs and clinical benefits of universal screening against no screening using the Markov model. Women without history of thyroid dysfunction were included in the model and screened for autoimmune thyroid dysfunction with TSH and TPO antibodies measurement. It was observed that screening with TSH saved \$102 and raised QALY by 5.84 d compared with no screening, while testing with TPO antibodies cost \$212 and raised QALY by 5.11

d compared with TSH screening. Likewise, Thung *et al.*<sup>[39]</sup> compared the two screening strategies in asymptomatic SCH during pregnancy; universal screening vs no screening using a decision analysis model. Women in the universal screening strategy were screened with TSH measurement and received LT<sub>4</sub> therapy if diagnosed with SCH. This analysis model showed that universal screening is cost-effective and that screening 100000 women during pregnancy saved \$8356383 and gained 589.3 QALYs.

The major limitation of these studies remains the fact that this analyses were based on data from observational trials, such as Haddow *et al.*<sup>[10]</sup> and Pop *et al.*<sup>[50]</sup>, rather than from RCTs. As a consequence, a universal screening approach should not be adopted based on what can be deemed as level 2 evidence. However, Dosiou *et al.*<sup>[64]</sup> recently conducted a cost-effectiveness study on screening asymptomatic pregnant women for autoimmune thyroid dysfunction based on data from RCTs. They used "TreeAge Pro" model to compare universal screening approach vs selective screening or no screening by measurement of TSH and TPO antibodies. This analysis demonstrated that universal and selective screenings were both cost-effective compared with no screening. The incremental cost-effectiveness ratio (ICERs) of universal screening was \$7138/QALY and that for selective screening was \$6753/QALY. In addition universal screening was found to be greatly cost-effective compared with selective screening, with an ICER of \$7258/QALY. This study is unique in that it is the only cost analysis model that used data from RCTs<sup>[8,65]</sup> regarding rates of the effect of treatment on adverse outcomes. Therefore, it would be wise to consider this analysis in future recommendations of universal screening for hypothyroidism during pregnancy.

#### **Is there an intervention that can lead to improvements in the outcomes?**

Levothyroxine (LT<sub>4</sub>) is currently the synthetic thyroid hormone of choice to treat hypothyroidism and is highly effective with very minimal risk for adverse complications<sup>[66]</sup>. A few studies have demonstrated a beneficial role of LT<sub>4</sub> therapy in reducing obstetric complications<sup>[6,65,67,68]</sup> and improving outcomes in women with SCH who had underwent *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI)<sup>[69]</sup>. However, in the Negro *et al.*<sup>[8]</sup> study, the reduced adverse outcome with therapeutic intervention was not statistically significant, and similar results regarding a lack of beneficial role of LT<sub>4</sub> therapy were obtained from another trial<sup>[53]</sup>. The conflicting results obtained could be related to the design of these studies, which were mostly observational and thereby limited their ability to provide robust evidence regarding the role of LT<sub>4</sub> therapy in pregnant women with SCH.

#### **Is there an appropriate test to screen for hypothyroidism during pregnancy?**

The TSH measurement with trimester-specific reference

limits is a first-line simple marker of thyroid dysfunction<sup>[19,20]</sup>. Studies have shown that the serum TSH estimation remains the most specific test to evaluate thyroid function, with greatly increased sensitivity upon using recent generation tests that utilize chemiluminescence labels rather than radio-isotopic substances<sup>[70]</sup>. Notably, serum TSH assays may not be sensitive enough in certain clinical scenarios, such as central hypothyroidism, adrenal insufficiency, renal failure, severe non-thyroidal illnesses and ingestion of certain medications<sup>[66]</sup>. In consideration of inaccuracy of TSH assays in these circumstances, it has been suggested to measure both TSH and FT<sub>4</sub> in all women for screening purposes.

FT<sub>4</sub> measurement distinguishes between SCH and OH and identifies cases of IH<sup>[71]</sup>. However, the gold-standard LC/MS/MS technique is too expensive and not routinely performed in most of the health facilities<sup>[49]</sup>. Consequently, the ATA recommends using other methods with consideration of different laboratory reference ranges<sup>[19]</sup>. Measurement of TPO antibodies may also be considered to identify euthyroid women with autoimmune disease and to predict later development of postpartum thyroiditis<sup>[71]</sup>. Due to significant risk of miscarriage and premature deliveries associated with positive TPO antibodies, some authors suggest to screen women for autoimmunity along with thyroid function early in pregnancy<sup>[65,72]</sup>.

#### **Is the TSH test acceptable to the population of women?**

TSH measurement in women during pregnancy is a less invasive procedure. It is accomplished by means of extracting blood sample with almost no harm to both mother and child, except for slight distress during the procedure. It is also timesaving when compared with other approved screening techniques, such as mammography and colonoscopy. There does, however, remain a possibility of inducing unfavorable effects on the mother, such as social stigma, stress and anxiety<sup>[39]</sup>.

## **TREATMENT OF HYPOTHYROIDISM DURING PREGNANCY**

There is no doubt that all pregnant women with OH should receive intervention with LT<sub>4</sub><sup>[6,19]</sup>. The evidence base for treating OH during pregnancy is derived from observational studies rather than RCTs, since allocation of some women to a non-treatment strategy would clearly be unethical<sup>[19]</sup>. On the other hand, there is no general agreement on treating women with SCH, isolated hypothyroxinaemia and euthyroid women with autoimmune hypothyroidism<sup>[11,19,20]</sup>. The lack of a general consensus in treating these specific conditions reflects the scarcity of interventional randomised trials that have tested the efficacy of treatment vs no treatment on adverse outcomes<sup>[19]</sup>.

#### **Beneficial effects of interventional therapy**

**LT<sub>4</sub> therapy:** The evidence for a clear benefit of LT<sub>4</sub>

therapy in pregnant women who are identified with mild hypothyroidism is controversial. Abalovich *et al*<sup>[65]</sup> showed that adequate LT<sub>4</sub> therapy aiming to maintain TSH level < 4.0 mIU/L reduced the rate of obstetric complications. In a secondary analysis of this trial, it was shown that in women who received adequate LT<sub>4</sub> therapy, the rate of preterm delivery was 1.6% compared with 12.5% in those inadequately treated ( $P = 0.05$ )<sup>[67]</sup>. Similarly, Tan *et al*<sup>[68]</sup> showed in a retrospective study that obstetric complications were less frequently encountered when hypothyroidism was treated compared with women who were euthyroid. However, being a retrospective study with the data derived from a single center limits the strength of evidence.

In a well-designed RCT, Negro *et al*<sup>[65]</sup> recruited 984 pregnant women to evaluate autoimmune hypothyroidism and the effect of LT<sub>4</sub> therapy in improvement of obstetrical adverse outcomes. Women with positive TPO antibodies were randomised into LT<sub>4</sub> intervention vs non-treatment strategies, and women with undetected TPO antibodies acted as a control strategy. They showed that in women treated with LT<sub>4</sub> therapy, the rate of miscarriage was 3.5% compared with 13.8% in women who were not treated ( $P < 0.05$ ). Similarly, the rate of premature deliveries was 7% compared with 22.4% in women not treated ( $P < 0.05$ ). However, the difference was not statistically significant with regards to other adverse obstetric outcomes.

In an attempt to evaluate the effect of LT<sub>4</sub> doses adjustments on TSH and FT<sub>4</sub> levels, Rotondi *et al*<sup>[73]</sup> enrolled 25 pre-conception women who were under treatment with LT<sub>4</sub> therapy and who were wishing to conceive and later confirmed pregnant. They showed that in hypothyroid women receiving modified doses of LT<sub>4</sub> therapy, there were significantly increased FT<sub>4</sub> and reduced TSH levels compared with women who remained under the same LT<sub>4</sub> doses before pregnancy ( $P = 0.001$ ). Similarly, Yassa *et al*<sup>[74]</sup> demonstrated that LT<sub>4</sub> therapy is effective in maintaining TSH concentration < 5.0 mIU/L during the first trimester. A significant reduction in TSH level below 0.5 mIU/L has been shown in 32% of women who received lower supplementary doses compared with 65% of women who received higher doses of LT<sub>4</sub> therapy ( $P < 0.01$ ).

Recently, in a large prospective randomised trial, women who received LT<sub>4</sub> therapy had fewer adverse outcomes than women who were not, but the difference was not statistically significant<sup>[8]</sup>. In another prospective randomised trial, it was demonstrated that LT<sub>4</sub> therapy significantly improved embryo implantation, live birth and miscarriage rates in women with SCH who underwent IVF/ICSI<sup>[69]</sup>. In contrast to these findings, Lazarus *et al*<sup>[53]</sup> failed to demonstrate a beneficial role of LT<sub>4</sub> therapy in improvement of neuropsychological abilities in 3 years old children born to mothers with high TSH or low FT<sub>4</sub> levels. Moreover, a recent Cochrane review of four RCTs showed that at present there is no sufficient evidence to support routine treatment with LT<sub>4</sub> of SCH during pregnancy<sup>[75]</sup>.

**Selenium therapy:** Another intervention used in recent years is the trace element selenium (also known as 21<sup>st</sup> amino acid), which has been shown to be beneficial in treating women with positive TPO antibodies to prevent thyroid inflammatory process<sup>[76]</sup>. In the thyroid tissue, the activity of glutathione peroxidase is dependent on the availability of selenium, and its deficiency predisposes to increased formation of free radical, hydrogen peroxide and lipid and phospholipid hydro-peroxides. These metabolic intermediates have destructive effects within thyroid tissue and also affect both humoral and cell-mediated immunity, increasing the possibility of autoimmune thyroiditis. Therefore, it has been suggested that selenium supplementation might have immune modulatory effects in autoimmune thyroiditis<sup>[77]</sup>. The number of studies testing selenium as a therapeutic intervention during pregnancy is limited. Negro *et al*<sup>[78]</sup> identified 169 out of 2143 pregnant women who screened positive for TPO antibodies. They noted a significant risk reduction of 28.6% in postpartum thyroiditis in the group of women who received selenium compared with 48.6% in the placebo group ( $P$  value < 0.01). A statistically significant ( $P$  value < 0.01) reduction of persistent maternal hypothyroidism in patients who received selenium (11.7%) was observed as compared with women who received placebo (20.3%). Benefits of selenium intervention were also evidenced by significant reduction in the TPO antibodies and improved thyroid ultrasonography findings in women who received selenium compared with the placebo group.

**Intravenous immunoglobulin therapy:** Clinical evidence on the use of intravenous immunoglobulin (IVIG) therapy in treatment of thyroid autoimmunity during pregnancy is scarcely available and conflicting. Kiprof *et al*<sup>[79]</sup> observed a reduction in circulating auto-antibodies and improvement of miscarriage rate in women with immunologic abnormalities suffering recurrent miscarriage. In a prospective non-randomized clinical trial, Stricker *et al*<sup>[80]</sup> evaluated 47 women with recurrent miscarriage who had multiple autoimmune diseases (53% were identified with thyroid autoimmunity). They found a significant difference in miscarriage rate between women treated with IVIG and women in the untreated group. In contrast, Vaquero *et al*<sup>[81]</sup> found a significant reduction in miscarriage rate in 11 women with thyroid auto-antibodies who received LT<sub>4</sub> therapy compared with 16 women treated with IVIG therapy.

#### **Who should be treated?**

In the setting of treating hypothyroidism, in accordance with ATA and Endocrine Society recommendations, all women diagnosed with OH during pregnancy should be treated with LT<sub>4</sub> therapy. However, treatment of pregnant women with SCH remains controversial. While the ATA guideline do not recommend LT<sub>4</sub> therapy in women with SCH and negative TPO antibody, the Endocrine Society recommends treating them regardless of thyroid

autoimmune status<sup>[19,20]</sup>. In addition, due to insufficient evidence suggesting harm, the ATA guidelines does not recommend treatment of isolated hypothyroxinemia in pregnant women<sup>[19]</sup>.

**Subclinical hypothyroidism:** Several observational studies have demonstrated a significant association between subclinical hypothyroidism (SCH) during pregnancy and obstetrical complications<sup>[7,12,59,60]</sup>. However, Cleary-Goldman *et al*<sup>[9]</sup> failed to demonstrate such association. These observational studies were mostly prospective, and the differences in results obtained could be related to using different biochemical definitions for SCH and various timing during gestation to test for TSH. One RCT by Negro *et al*<sup>[8]</sup> found a significant reduction in the rate of obstetrical complications in women with SCH during pregnancy when these women were treated with LT<sub>4</sub> therapy.

The cognitive and neurophysiologic outcomes in offspring born to mothers with SCH have also been tested in several studies, and the results were controversial. The largest observational study of Haddow *et al*<sup>[10]</sup> showed a significant reduction in IQ scores by 7 points among women with SCH compared with controls. Smit *et al*<sup>[82]</sup> in a small prospective observational study demonstrated a significant reduction in the mean mental developmental index (MDI) in children born to mothers with SCH compared with children of euthyroid mothers. Similarly, in another small prospective observational study, Li *et al*<sup>[14]</sup> showed a significant reduction in the Bayley's scale scores and the MDI of children born to women with SCH compared with children born to women with maternal euthyroidism. On the contrary, Lazarus *et al*<sup>[53]</sup> did not find a significant difference in improvement of IQ of children born to women with SCH who had received LT<sub>4</sub> therapy compared to children of women in the control group.

**Euthyroid status with autoimmune hypothyroidism:** In iodine replete regions, autoimmune thyroiditis remains the most common cause of hypothyroidism during pregnancy<sup>[75]</sup>. Autoimmune thyroiditis is defined as the presence of increased levels of TPO and TGAb antibodies in the circulation of pregnant women<sup>[83]</sup>, but TPO antibodies are considered distinctive and the most sensitive marker<sup>[84]</sup>.

Several studies have observed the presence of thyroid auto-antibodies in euthyroid mothers associated with adverse obstetric complications; however, these results are inconsistent. In an observational case-control study, Bussen *et al*<sup>[85]</sup> found a significant increase in the incidence of thyroid auto-antibodies in women who presented with a history of recurrent abortions. A Finnish prospective population-based study found that women with TPO and TGAb antibodies had two to three times increased risk of perinatal mortality compared with antibody negative women, regardless of TSH and FT<sub>4</sub> levels<sup>[86]</sup>. A meta-analysis of observational studies

reported an odds ratio (OR) of 2.73 for miscarriage in women with thyroid autoimmunity in eight case-control studies and OR of 2.30 in ten longitudinal studies<sup>[76]</sup>. Similarly, a recent meta-analysis found the OR for miscarriage in case-control and prospective studies to be 2.55 and 2.31, respectively<sup>[87]</sup>. In another recent meta-analysis, Thangaratinam *et al*<sup>[88]</sup> showed an OR of 3.90 and 1.80 for miscarriage in women with autoimmune thyroiditis in prospective cohort studies and in case-control studies, respectively. In a prospective randomized trial, Negro *et al*<sup>[89]</sup> showed a significant increased risk of miscarriage in women with positive TPO antibodies and subfertility undergoing assisted fertilization. In a meta-analysis, Toulis *et al*<sup>[83]</sup> demonstrated a significant two-fold higher risk for miscarriage in women with thyroid auto-antibodies compared with women in the control group ( $P < 0.001$ ).

The cognitive and neurologic development in children born to euthyroid mothers with thyroid auto-antibodies has also been investigated. In a prospective study, Pop *et al*<sup>[90]</sup> reported a significant reduction on the McCarthy's scale scores in children born to euthyroid mothers with positive TPO antibodies compared with mothers who screened negative for TPO antibodies. In a recent retrospective case-control study, Li *et al*<sup>[14]</sup> used stored blood samples from a group of Chinese women who were screened for Down syndrome in 2004. They observed that the mean intelligence and the mean motor scores on the Bayley's scale of 34 children were 10.56 and 9.03 points lower than that of 142 children in the control arm, respectively ( $P = 0.001$  in both). However, being retrospective in design, it would be difficult to avoid important confounders such as parental IQ, which might affect the intellect of children. Based on data derived from 3139 women within the Generation R Study, Ghassabian *et al*<sup>[84]</sup> reported an OR of 1.64 for externalizing disorders in the offspring (age 3 years) of women with increased levels of TPO antibodies compared with children born to women with negative TPO antibodies ( $P$  value = 0.004). In contrast, children born to women with positive TPO antibodies did not show significant delayed language development (including vocabulary and phrase development) and nonverbal cognitive delay at the age of 3 years.

Treatment with LT<sub>4</sub> therapy may improve miscarriage rates in women with thyroid autoimmunity, however, the results are inconsistent. For instance, in a well-designed RCT, Negro *et al*<sup>[65]</sup> demonstrated a significant reduction in the rate of miscarriage and premature deliveries upon treatment with LT<sub>4</sub> therapy in women with positive TPO antibodies during pregnancy. Previously, Negro *et al*<sup>[89]</sup> did not find that LT<sub>4</sub> therapy improved miscarriage rate. However, a meta-analysis of both studies revealed a significantly reduced relative risk of 52% in miscarriage rate upon treatment with LT<sub>4</sub> therapy<sup>[88]</sup>.

**Isolated hypothyroxinemia:** The association between isolated hypothyroxinemia (IH) during pregnancy and

obstetrical complications is controversial. Casey *et al*<sup>[91]</sup> identified 233 out of 17298 pregnant women with IH and found no associated increased risk of obstetric complications. In contrast, Cleary-Goldman *et al*<sup>[9]</sup> found in their secondary analysis a significant association of IH and increased risk of preterm labor, macrosomia and GDM.

Recent evidence suggests that IH may adversely affect offspring's cognitive and neurologic outcomes, although the results are equivocal. In a prospective observational study, Pop *et al*<sup>[13]</sup> showed a significant reduction in the mental and motor functions of the Bayley's scale scores in the offspring of women with IH compared with those of the offspring of women in the control group. Similarly, in a small prospective observational study, Li *et al*<sup>[14]</sup> showed a significant reduction in the intelligence and motor scores of children born to women with IH compared with children born to women with maternal euthyroidism. Recently, Henrichs *et al*<sup>[5]</sup> showed in the largest prospective Generation R study (a population-based cohort) that there was a significant risk of impairment in expressive language and nonverbal cognition in children born to mothers with IH. However, the assessment of children's cognitive development in this study was totally dependent on mothers reporting, a fact which might increase the risk of observer bias. In contrast, Lazarus *et al*<sup>[53]</sup> did not show a significant difference between the children's IQ of women with IH who received LT<sub>4</sub> therapy as compared to the control group. This randomized trial had several criticisms though, including significant loss to follow-up. Similarly, in an observational case-control study, Craig *et al*<sup>[92]</sup> found that the Bayley's scale scores of children born to women with FT<sub>4</sub> level below the 3<sup>rd</sup> percentile did not differ significantly from scores of children born to women with FT<sub>4</sub> level between the 10th and 90th percentile.

### **Hypothesis-1**

From the foregoing discussion it is obvious that screening pregnant women for hypothyroidism meets most of the Wilson and Jungner criteria that justify screening for disease. However, the evidence of associated adverse outcomes is not clear enough. There is also a lack of good quality evidence regarding impact of maternal subclinical hypothyroidism on neuropsychological development in children. The association of maternal hypothyroidism with obstetric complications also remains contentious. In addition, the evidence for a clear benefit of therapeutic intervention in pregnant women with mild hypothyroidism is also not convincing. Inadequacy of clear evidence for both associated adverse complications and efficacy of intervention may partially act against Hypothesis-1. Studying the impact of screening and treatment on improvement of children neurocognitive status and obstetric complications in large RCTs will be important to understand further the impact of milder thyroid under-activity upon outcomes for mother as well

as the child.

On the other hand, previous cost analyses models were based on data from observational studies, unlike recent models that used data from RCTs. The recent analysis model of Dosiou *et al*<sup>[64]</sup> supports the cost-effectiveness of universal screening. This significant study supports Hypothesis-1 and could potentially influence feasibility to adopt universal screening for hypothyroidism during pregnancy. Moreover, hypothyroidism during pregnancy should be considered an important health issue with wide-spread prevalence as per the study of Blatt *et al*<sup>[17]</sup>. Further inclusion of women with EAD and IH adds further weight in favour of Hypothesis-1.

The screening program will identify both overt as well as subclinical hypothyroidism and other subtypes. There is level 1 evidence that suggests adverse maternal and foetal outcomes if overt hypothyroidism remains untreated in pregnancy; on the other hand, there is lack of evidence on the beneficial impact of therapeutic intervention in subclinical hypothyroidism. Therefore, universal screening, if cost effective, will improve obstetric as well as foetal outcomes in a subset of patients (overt hypothyroidism) even though the other subgroup (subclinical hypothyroidism) may not be benefited by this approach. Although screening for hypothyroidism during pregnancy does not satisfy most of the Wilson and Jungner criteria for a standard screening test, it is difficult to rationalize only a "high risk" screening approach for this condition associated with maternal as well as neonatal morbidity. It is worthwhile to note that the patient population to screen is already well defined (cohort of pregnant women), which further enhances cost effectiveness. In addition, the easy access of the TSH test as an appropriate tool and acceptability to the population of women may further augment justification of screening and supports Hypothesis-1.

### **Hypothesis-2**

We have reviewed the available literature to evaluate complications and efficacy of intervention in SCH, IH and euthyroid women with autoimmune hypothyroidism during pregnancy. To discuss and analyze Hypothesis-2, these three sub-groups will be discussed separately.

Firstly, observational studies in women with SCH are not homogenous with regard to using different biochemical definitions for SCH and different timing to test for TSH. Therefore, the quantity and consistency of data are suggestive, although not conclusive, in demonstration of an association with adverse obstetrical complications. These studies suggest a possible association of SCH and increased risk of hypertensive disorders, pregnancy loss, abruptio placentae and preterm delivery<sup>[7,12,59,60]</sup>, but Cleary-Goldman *et al*<sup>[9]</sup> found no such association. It could be possible that the increased risk for adverse obstetrical outcomes in women with SCH in these studies was a consequence of an additive effect of women being at risk to develop these

complications. The women populations in Negro *et al*<sup>[60]</sup> were Caucasian Italian and that in Casey *et al*<sup>[7]</sup> were medically indigent from a single hospital, and as such, the generalizability of their findings remains a genuine concern. In addition, the population in Cleary-Goldman *et al*<sup>[9]</sup> belongs to heterogeneous backgrounds.

On the other hand, evidence from one RCT convincingly demonstrated that LT<sub>4</sub> therapy promoted improvement of adverse obstetric complications in women with SCH (Negro *et al*<sup>[8]</sup>). The data of this study were used in the recent cost effectiveness analysis by Dosiou *et al*<sup>[64]</sup>, which demonstrated that universal screening is clearly cost-effective based on the rates of the effect of LT<sub>4</sub> therapy on adverse outcomes. The evidence obtained from this RCT and the cost effectiveness analysis supports Hypothesis-2 with regard to the benefits of treating SCH in pregnant women. The evidence for impaired cognitive outcomes in offspring born to mothers with SCH was obtained mostly from observational studies<sup>[10,14,82]</sup>, but intervention with LT<sub>4</sub> therapy in a prospective randomised trial has not shown beneficial impact in improving cognitive outcomes<sup>[53]</sup>. However, there are two important drawbacks of this study: the significant loss to follow-up and the late initiation of LT<sub>4</sub> therapy during gestation. Therefore, with regards to cognitive outcomes, it seems difficult to support Hypothesis-2 based on evidence derived mainly from observational rather than well-designed RCTs.

Secondly, observational studies showed that thyroid autoimmunity has been linked with an increased risk of habitual abortion, miscarriage, preterm delivery and increased risk of perinatal mortality<sup>[85,86]</sup>. These observations were further supported by a prospective randomized trial (but not placebo controlled) of Negro *et al*<sup>[89]</sup> and four recent meta-analysis of observational and cohort studies<sup>[76,83,87,88]</sup>. This significant association does not infer a causal relationship between autoimmune thyroiditis and risk of miscarriage because other autoimmune diseases, such as antiphospholipid syndrome and systemic lupus erythematosus, could also influence pregnancy outcomes. Impaired cognitive outcomes in offspring born to mothers with thyroid autoimmunity were demonstrated in observational studies<sup>[14,90]</sup>. However, this was not the case in the recent Generation R Study<sup>[84]</sup>. Although large, prospective and population-based, the main drawback of this study is that, unlike previous studies, the assessment of children's cognitive development was totally dependent on parental subjective assessment, a fact that might increase the possibility of an observer bias. However, both father and mother were asked separately to report on their child's behavior, and both were blinded to the results of thyroid function. A benefit of intervention with LT<sub>4</sub> therapy was not clear and inconsistent<sup>[65,88,89]</sup>. In view of the limited number of studies investigating the effect of LT<sub>4</sub> therapy in euthyroid women with autoimmune disease and their smaller sample size, it is difficult to make a clear conclusion of effectiveness. However, the trend for reduced miscarriage and preterm delivery in women treated with

LT<sub>4</sub> therapy may suggest a beneficial role. On the other hand, use of other interventions, such as selenium and IVIG therapies, to treat thyroid autoimmunity in pregnant mothers has not been extensively studied, and results are conflicting. Moreover, the beneficial results obtained need validation in a larger group of women using well-designed trials, bearing in mind the issues of safety and cost effectiveness. Therefore, in view of these findings regarding the benefits of intervention in euthyroid women with thyroid autoimmunity and lack of RCTs and cost effectiveness analyses, it seems unjustifiable to support Hypothesis-2.

Finally, the results of observational studies investigating the association of IH with adverse obstetrical outcomes<sup>[9,91]</sup> and that with adverse cognitive and neurological outcomes<sup>[5,13,14,53,92]</sup> have been inconsistent. In addition, there has been no improvement in cognitive and neurological outcomes in children born to mothers with isolated hypothyroxinaemia upon intervention with LT<sub>4</sub> therapy<sup>[53]</sup>. Therefore, in view of these findings and a lack of clear evidence indicating poor outcome of isolated hypothyroxinaemia, it seems difficult to recommend firmly treating this condition during pregnancy. Moreover, routine FT<sub>4</sub> immunoassays are affected by elevated TBG and other binding proteins, whereas the gold-standard LC/MS/MS technique is not available in most of the health facilities<sup>[48]</sup>. Consequently, choosing appropriate candidates for treatment based on accurate FT<sub>4</sub> measurements might not be cost effective, and it remains difficult to support Hypothesis-2.

## CONCLUSION

In conclusion, screening asymptomatic women for mild thyroid dysfunction during pregnancy could offer an opportunity to initiate early intervention and to obtain further epidemiological data to evaluate natural history of SCH. It is clear that carrying out universal screening to identify the varieties of hypothyroidism during pregnancy meets most of the general criteria that justify screening for a disease. Hypothyroidism during pregnancy could be considered an important health issue when SCH, IH and euthyroid women with autoimmune hypothyroidism were included in the diagnosis, using the recent ATA definitions. Moreover, universal screening was found to be greatly cost-effective compared with selective screening in a recent cost analysis. However, an important limitation in studies involving cost utility analysis is the lack of prospective experimental trials evaluating the effects of treatment against no treatment on neuropsychological development in children born to women with hypothyroidism. In addition, the evidence of associated adverse outcomes was also not conclusive due to a lack of well-designed randomised trials testing the evidence of a clear benefit of intervention. Few RCTs demonstrate that LT<sub>4</sub> therapy promotes improvement of adverse obstetric complications in women with SCH, but the evidence for impaired cognitive outcomes is

inconsistent. Similarly, it is also difficult to make a clear conclusion of LT<sub>4</sub> therapy effectiveness in cases of thyroid autoimmunity and isolated hypothyroxinaemia based on observational studies. Nevertheless, it seems justifiable to treat all women with SCH during pregnancy with LT<sub>4</sub> therapy, same as women with OH. In addition, because of uncertainty of a possible beneficial role of intervention in thyroid autoimmunity and isolated hypothyroxinaemia, it seems difficult to advise for or leaving aside treating these conditions. The conclusion drawn from most of the trials conducted has been limited by lack of statistical power and the controversial results obtained. In the future, the most favorable trial would be expected to test women with SCH, IH and thyroid auto-antibodies during pregnancy. Ideally this trial should have a larger population of different ethnic backgrounds, be double-blinded and include a well matched control group. A relatively longer follow-up of children born to mothers with SCH would be crucial to evaluate cognitive and neurological outcomes.

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