Thyroid disease in pregnancy and screening

Shahzad Ahmed (1)
Kashif Ali Raza (2)

(1) Consultant Family Medicine – Primary Healthcare Corporation (PHCC) Qatar, Sessional GP UK

Corresponding author:
Dr Shahzad Ahmed MBChB, MRCGP
Consultant Family Medicine
Primary Healthcare Corporation (PHCC) Qatar,
Sessional GP UK
Email: shaahmed@phcc.gov.qa

Abstract

Thyroid dysfunction in the form of hypo and hyper-thyroidism are some of the most common endocrine conditions encountered in primary care. The hormone deficiency or excess can be easily diagnosed and managed yet is potentially fatal in severe cases if left untreated. Detection of thyroid dysfunction becomes even more important in pregnant women because it can lead to various complications and adverse outcomes for the mother and foetus. Clinical manifestations of thyroid dysfunction can range from life threatening to no signs or symptoms. Furthermore, often, the non-specific symptoms can be difficult to differentiate from symptoms related to normal physiological changes in pregnancy that women often experience. Primary care physicians are the first point of contact for women when they become pregnant. Therefore, it's important that clinicians are able to confidently diagnose and manage these conditions at the earliest opportunity by organising thyroid function tests and seeking specialist input where necessary. However, guidelines around the world advocate various approaches to decision making about testing pregnant women for thyroid disease. There is increasing debate about whether thyroid screening should be made universal. In this article we look at the current guidelines and latest evidence and opinion in this important area.

Key words: thyroid disease, pregnancy, screening

Introduction

There are significant changes to thyroid physiology during a normal pregnancy. Early foetal and placental growth relies on availability of adequate maternal thyroid hormone. In response to the increased metabolic demand, the size of the thyroid gland in pregnant women increases by about 10% in parts of the world with adequate dietary iodine, and 20-40% in countries where there is iodine deficiency. When there is thyroid dysfunction in pregnancy, it is classified as hypo or hyperthyroidism and further subcategorised as either overt or subclinical (Table 1). Over the last few decades, observational studies have shown that maternal thyroid dysfunction, in the form of overt, subclinical and autoimmune disease states is associated with adverse outcomes for the mother and the foetus. At the same times, studies have also shown that there is clear improvement in outcomes when overt maternal hypo and hyperthyroidism are treated. Although subclinical hypothyroidism is much more common than overt hypo or hyperthyroidism, the picture is not as clear when it comes to the benefits in its detection and subsequent treatment with levothyroxine. This has resulted in considerable debate around the world about universal thyroid screening for pregnant women.

Understanding thyroid function in pregnancy

In pregnancy in order meet the increased metabolic demands of the body, there are significant changes in thyroid physiology which can be seen in the form of altered thyroid hormones level (1). Therefore, thyroid function tests of pregnant women will be different from those of healthy non pregnant women. From conception there is an increase in serum hCG levels which peak around 10-12 weeks of gestation. During the first trimester, this maternal hCG directly stimulates the TSH receptor which increases thyroid hormones production. The total serum T4 and T3 concentrations increase with a slight increase in serum free T4 and T3 within the normal range. In response to this increased production in thyroid hormone levels, the thyroid axis negative feedback leads to decreased serum TSH concentrations (2). Pregnant women will therefore have lower serum TSH concentration compared to before pregnancy. Although widely accepted that there is a decrease in TSH concentration in early pregnancy in all populations, studies have shown that there are significant variations in terms of the extent of this reduction in different racial and ethnic groups. Due to this variation in thyroid hormone levels during different stages of pregnancy and amongst different population groups, the American Thyroid Association (ATA) for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum 2017 guidelines recommend using population based, trimester specific reference ranges for TSH and serum T4 (3). Many labs around the world do not provide trimester specific ranges, in which case ATA recommend that TFTs are interpreted as such that;

• In weeks 7-12 – reduce the lower limit of the reference range of TSH by approximately 0.4mU/L and upper limit by 0.5 mU/L (corresponding to a TSH reference range of approximately 0.1 to 4mU/L).
• In the second and third trimester – there should be a gradual return of TSH towards the non-pregnant normal range

Serum TSH remains the initial and most reliable test that is available for assessing thyroid function in pregnancy. Furthermore, its widely available and relatively inexpensive. In ATA's previous guidelines in 2011, the recommendation for upper reference limit of TSH in first trimester was 2.5mU/L and for the 2nd and 3rd Trimesters it was 3.0mU/L. If the TSH is outside the trimester specific range then FT4 and FT3 levels should also be measured. Thyroid peroxidase antibodies (TPOAb) and TSH receptor antibodies (TRAb) can also be checked to confirm autoimmunity which is the commonest cause of thyroid dysfunction.

Hyperthyroidism in pregnancy

Overt hyperthyroidism is relatively uncommon in pregnancy and is defined as serum TSH levels below the trimester specific reference range with elevated free T3, T4 or both. This occurs in approximately 0.1%-0.4% of pregnancies (4). Although hyperthyroidism from any cause can be potentially detrimental to the pregnancy, Graves' disease and hCG mediated hyperthyroidism are the 2 most common causes of hyperthyroidism in pregnant women (5). Although a definitive diagnosis may not be easy at the outset, the differential diagnosis in early pregnancy in the majority of the cases is usually between these two conditions. The primary aim should be to differentiate between the two. This is done through a combination of careful history, examination and analysis of the thyroid function test. Some of the symptoms suggestive of hyperthyroidism can be similar to the nonspecific symptoms associated with pregnancy such as; heat intolerance, increased perspiration and tachycardia. More specific symptoms can include tremor, anxiety, weight loss with normal appetite. Examination findings such as presence of goitre or eye signs could be more suggestive of Grave's disease.

When there is history of thyroid disease, risk factors or clinical suspicion in women who are trying to conceive or have become pregnant, then serum TSH level should be measured (Figure 1). If the TSH level is <0.1 mU/L then free or total T4 and T3 measurements should be obtained. The diagnosis of overt hyperthyroidism can be confirmed with a suppressed (<0.1mU/L) or undetectable TSH (<0.01 mU/L) and free T4/T3 levels that are above the normal range for pregnancy. If TRAb are measured and present then that will be indicative of Graves' disease. Further investigations such as radioiodine scans are contraindicated, therefore careful history and examination is vital in establishing the cause of hyperthyroidism. Without prior thyroid disease and absence of signs such as a goitre or thyroid eye disease hCG mediated hyperthyroidism is more likely the cause of suppressed TSH. There are couple of variants of hCG mediated hyperthyroidism which include;

Gestational transient thyrotoxicosis; which occurs towards the end of first trimester and is characterised by slightly low TSH levels and mildly elevated free T4 concentrations. This form of subclinical hyperthyroidism or mild overt hyperthyroidism is related to the peak in hCG levels around weeks 10-12. This phenomenon is transient and does not require treatment with antithyroid drugs and typically resolves as hCG production tails off after the first trimester.

Table 1 – summarises the changes in thyroid hormones in different forms of thyroid dysfunction

Type of thyroid dysfunction	Laboratory findings
Overt hypothyroidism	High TSH, low fT4
Subclinical hypothyroidism	High TSH, normal fT4
Overt hyperthyroidism	Low TSH, high fT4
Subclinical hyperthyroidism	Low TSH, normal fT4

Hyperemesis gravidarum; is a syndrome whereby the pregnant women will experience vomiting due to the presence of higher hCG and oestradiol levels compared to normal pregnant women. TSH levels will be suppressed in these women due to the thyroid stimulating effect of the hCG. Some of these women will also have higher serum free T4 concentrations resulting in overt hyperthyroidism. Vomiting with absence of other signs and symptoms of hyperthyroidism helps to distinguish this from other causes. Again, this is transient and is expected to resolve by the end of the first trimester. Only symptomatic treatment for the vomiting is required and there is no role for antithyroid drugs.

Pregnant women in whom overt hyperthyroidism (most often due to Graves' disease) is not corrected are at increased of spontaneous miscarriage, congestive heart failure, thyroid storm, preterm birth, pre-eclampsia, foetal growth restriction and increased perinatal morbidity and mortality (6-8). Treatment options include carbimazole, methiamazole or propylthiouracil. These block the thyroid hormones synthesis and reduce titre of TSH receptor antibodies. There is in indecision in literature about the choice of drugs for hyperthyroidism in pregnancy. Primary care physicians are likely to need input from specialists in the management of pregnant women with Graves' disease.

Hypothyroidism

Overt hypothyroidism in pregnancy is defined as having an elevated population and trimester specific TSH concentration with reduced free T4 concentration. According to ATA 2017 guidelines when local reference ranges are not available an upper limit of TSH can be set at 4mU/L (3). The prevalence of hypothyroidism is estimated to be around 2% whilst 0.5% of all pregnant women will have overt hypothyroidism (9,10). The most common cause of hypothyroidism in pregnancy is chronic autoimmune thyroiditis (Hashimoto's disease). Other less common causes include iodine deficiency, previous radioactive iodine therapy and thyroidectomy.

Clinical symptoms of hypothyroidism during pregnancy is similar to those that non pregnant women experience, which can include general tiredness, cold intolerance, constipation and weight gain. Some women will not have any symptoms at all whereas in others it may be mild and difficult to differentiate from physiological changes attributed to the pregnancy.

Over the last few decades observational studies have consistently shown that untreated overt hypothyroidism has been associated with increased risk for adverse pregnancy complications. As well as the classic detrimental effects on foetal neurocognitive development, some of the other complications include increased risk of miscarriage, premature births, low birth weight and gestational hypertension (11-13). Due to these well-established associations between overt hypothyroidism and risk to the mother and foetus, it is essential that this condition is detected and treated at the earliest opportunity with levothyroxine to stabilise the maternal serum TSH levels within recommended trimester specific reference range. ATA recommend that 'parallel to treatment of hypothyroidism in (the) general population, it is reasonable to target a TSH in the lower half of the trimester-specific reference range. When this not available, it is reasonable to target maternal TSH concentration below 2.5mU/L' (3).

Subclinical Hypothyroidism

In the last few decades subclinical hypothyroidism has emerged as a clinical topic which has generated a great deal of attention and debate especially when considered in pregnant women. It has become a stumbling block when it comes to recommending universal screening for thyroid dysfunction in pregnancy. In context of pregnancy, its incidence is more common than overt hypothyroidism, with an estimate from 15-28% in regions where there is no iodine deficiency (14). One of the main issues has been in defining subclinical hypothyroidism because there has been a lack of agreement amongst societies around the world about what cut off values are to be applied to TSH levels. As per ATA 2017 guidelines subclinical hypothyroidism can be defined by a normal free T4 in the presence of elevated TSH concentration (3). The upper limit of normal TSH is different in each trimester and should be defined by local laboratories to reflect the population demographics. However, it is recognised that population derived trimester specific data and reference ranges will not be widely available in which case an upper limit of 4.0mU/L can be used (3). To highlight the difficulty in defining and diagnosing subclinical hypothyroidism, it is to be noted that ATA's 2017 reference ranges for TSH are higher than the previous guidelines in 2011.

In subclinical hypothyroidism the risk of complications is lower compared to pregnant women who have overt hypothyroidism. However, there have been numerous studies in which women with subclinical hypothyroidism were at higher risk of severe preeclampsia, placental abruption, preterm delivery, neonatal respiratory distress syndrome and miscarriage in comparison to euthyroid women (15-19). These risks in mildly elevated TSH become even higher in the presence of thyroid peroxidase antibodies (TPOAb). Therefore, ATA recommends testing of TPOAb in pregnant women who have a TSH level above 2.5mU/L.

Whilst there are many studies which have demonstrated the increased risks associated with subclinical hypothyroidism, only a few small studies have actually been done to investigate the impact of treatment with levothyroxine in these women. Therefore, the treatment of pregnant women who have subclinical hypothyroidism with levothyroxine is just as controversial as its diagnosis. ATA recommends consideration for treatment with levothyroxine in subclinical hypothyroidism when TSH level is greater than 2.5mU/L with the presence of TPOAb or TSH level above 10mU/L without TPOAb (Figure 1). The ATA 2017 guidelines suggest that treatment of subclinical

Figure 1: Testing for thyroid function in pregnancy with references ranges – from ATA guidelines (3)

Screening
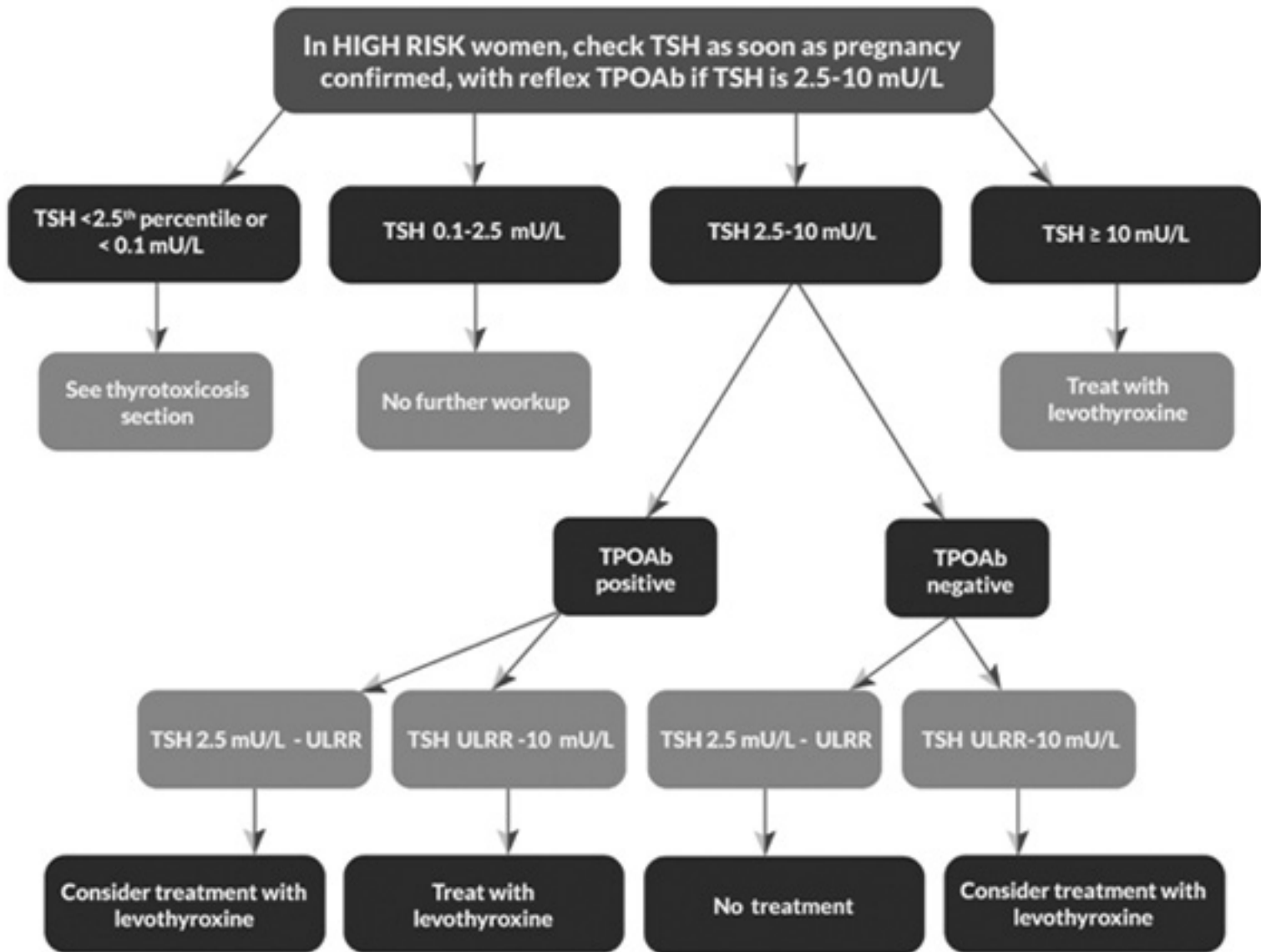
hypothyroidism in pregnant women, especially those with TPOAb may reduce the risk of adverse outcomes (3). However, it is not clear whether the treatment with levothyroxine actually reduces the risk of complications for the mother and baby in this situation. One of the limitations of the data from some of the studies is the start of levothyroxine treatment after the first trimester, which could be too late. A metanalysis of 18 studies in 2016 acknowledged that 'subclinical hypothyroidism during pregnancy is associated with multiple adverse maternal and neonatal outcomes. The value of levothyroxine therapy in preventing these adverse outcomes remains uncertain' (20). However, ATA does acknowledge despite the limitations of data from interventional trials for treatment of subclinical hypothyroidism, the aggregate data available does suggest benefit of treatment. The task force also acknowledged the very low risk in initiating low dose treatment with levothyroxine 50 micrograms.

The issue of screening for thyroid disease either before or during pregnancy is a controversial one which experts continue to debate around the world. Screening is defined by WHO as the presumptive identification of recognised disease in an apparently healthy, asymptomatic population by means of test or examinations that can be applied rapidly and easily to the target population (21). Before universal screening can be recommended, the condition for which screening is being suggested must fulfil the WHO 10-point criteria for screening. This is based on a report called 'Principles and Practice of Screening for Disease', by James Wilson and Gunner Jungner in 1968 (Table 2).

The idea of screening for thyroid dysfunction in pregnancy is keenly debated by those for and against it. Those in favour argue that careful analysis of these 10 criteria provides a persuasive case for universal thyroid screening in pregnancy. For criteria 1, it is well established that thyroid dysfunction, particularly untreated overt thyroid disease and autoimmunity in pregnancy are associated with adverse maternal and foetal outcomes and are therefore an important health problem. Furthermore, in pregnant women with overt hypothyroidism who are not diagnosed, the majority will remain hypothyroid after pregnancy, with a mean time to diagnosis in one of the studies being 5 years (23). Treatment of both hypothyroidism and hyperthyroidism results in improved outcomes with treatment and testing being both acceptable and widely available (criteria 2, 3, 5 and 6). For hypothyroidism in particular, there is a well-recognised latent asymptomatic stage (criteria 4 and 7). Thyroid status can be accurately assessed with inexpensive and widely available measurement of TSH, fT4 Levels and TPOAb. The cost of universal thyroid screening is favourable even if only the overt disease is considered (criteria 9). Also, the nature of screening in pregnancy ensures that it will be a continuous process (criterion 10).

However, those against universal thyroid screening argue that screening struggles to meet criterion 8 as a policy on whom to treat is yet to be agreed. Whilst all societies around the world would recommend treatment of overt thyroid disease, there is much greater debate about treating subclinical hypothyroidism with levothyroxine. They argue that overt thyroid dysfunction is less common than subclinical dysfunction and can be identified by clinical assessment and subsequent testing based on risk factors. Therefore, the biggest impact of universal screening would be identification of a large proportion of patients with subclinical hypothyroidism.

The main issue in the context of screening seems to be related to the lack of consistent evidence for treatment and effectiveness amongst the population of pregnant women with subclinical hypothyroidism. Whilst retrospective studies have shown some benefit in treatment with levothyroxine, this has not been replicated in prospective trials (23,24). A RCT by Negro and colleagues investigated the benefit of universal screening of pregnant women and the subsequent treatment when they had a TSH level of >2.5mU/L. In this study they randomised 4,500 women to universal screening versus screening of women at high risk of thyroid disease. Those women who were positive for TPOAb and had a TSH>2.5 mU/L were treated with levothyroxine in the first trimester. The study showed that there was no significant difference in adverse outcomes between the universally screened cohort versus those women who underwent high risk screening (25). Furthermore, results of the TABLET trial from UK that ATA 2017 guidelines refer to, have also been published in 2019 which concluded that, 'the use of levothyroxine in euthyroid women with thyroid peroxidase antibodies did not result in higher rate of live births than placebo' (26). One of the largest prospective studies on 22,000 women,

investigated the effect of treatment with levothyroxine on maternal hypothyroidism in early pregnancy. This study provided high quality evidence that hypothyroidism was far more likely to be diagnosed during pregnancy when women were screened (measurement of TSH and/or fT4) compared to with no screening. The incidence of hypothyroidism was 4.5% in the screened population and 5% in the unscreened group who had their TSH and fT4 samples stored until after birth, at which point 5% were diagnosed with hypothyroidism. Although, higher rates of hypothyroidism were diagnosed, there were no obvious difference between the two groups in terms of preterm births, low birth weight in the new born, or any neurocognitive disability at age of 3 (27).

Another study that was ongoing at the time the ATA guidelines were published in 2017 was a multicentre, RCT conducted by the National Institute of Health in the US. This study was evaluating the effect of levothyroxine treatment in pregnant women with subclinical hypothyroidism on the children's neurocognition. The results of the study also revealed that, 'treatment for subclinical hypothyroidism or hypothyroxinaemia at the beginning, between 8 and 20 weeks of gestation, did not result in significantly better cognitive outcomes in children through 5 years of age than no treatment for those conditions' (28).

ATA 2017 guidance with regards to screening for thyroid dysfunction concluded that; 'There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy' (3). Instead, the advice is all women planning pregnancy or newly pregnant should have a clinical assessment and if they have risk factors for thyroid disease then they should be offered serum TSH test.

Both the American College of Obstetricians and Gynecologists (ACOG) (2015) and the ATA 2017 clinical practice guidelines support screening of women at high risk for thyroid dysfunction before they become pregnant, or early in pregnancy (29,3). The European Thyroid Association guidelines concur with the ATA and ACOG regarding universal screening. However, these guidelines note that while not formally recommended, most of the authors support universal screening given that a substantial number of women with thyroid dysfunction may be missed with targeted screening strategies (30, 3). This was confirmed in a survey conducted in Maine which showed that many practitioners have already implemented routine TSH testing in pregnant women (30). A European survey found similar results, with 42% of responders screening all pregnant women for thyroid dysfunction (31). In fact, some countries like Spain, China and Poland are already recommending universal thyroid screening for pregnant women (32-34).

Table 2: World Health Organisation Screening Principles (Wilson & Jungner, 1968) (22).

1	The condition sought should be an important health problem
2	There should be an accepted treatment for patients with recognised disease
3	Facilities for diagnosis and treatment should be available
4	There should be a recognisable latent or early symptomatic stage
5	There should be suitable test or examination
6	The test should be acceptable to the population
7	The natural history of the condition, including development from the latent to declared disease should be adequately understood
8	There should be agreed policy on whom to treat as patients
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to the possible expenditure on medical care as a whole
10	Case findings should be a continuous process and not a "once and for all" project.

Table 3: List of risk factors for thyroid dysfunction screening in pregnancy (3)

1.	A history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
2.	Known thyroid antibody positivity or presence of a goitre
3.	History of head or neck radiation or prior thyroid surgery
4.	Age >30 years
5.	Type 1 diabetes or other autoimmune disorders
6.	History of pregnancy loss, preterm delivery, or infertility
7.	Multiple prior pregnancies (≥2)
8.	Family history of autoimmune thyroid disease or thyroid dysfunction
9.	Morbid obesity (BMI ≥40 kg/m2)
10.	Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
11.	Residing in an area of known moderate to severe iodine insufficiency

Conclusion

From observational and prospective studies over the last 3 decades, it has been well established that thyroid dysfunction can significantly impact a pregnant woman and her child. Thyroid dysfunction is common in women of child-bearing age and also results in substantial adverse obstetric and child neurodevelopmental outcomes. Furthermore, thyroid dysfunction can be readily diagnosed with reliable blood tests and easily corrected with inexpensive and available treatments, resulting in decreased rates of adverse outcomes. Given the dependence of the developing foetus on adequate maternal thyroid function, especially in early pregnancy, as well as the severity of outcomes in untreated thyroid disease, it makes sense for screening to take place as early as possible so that appropriate treatment can be administered without delay.

Universal screening for thyroid disease in pregnancy can identify patients with thyroid disease requiring treatment, and ultimately decrease rates of complication. The issue, therefore forms key debate in the world of thyroidology and obstetrics. American and European guidelines recommend screening only high-risk patients, which would appear to miss the majority of cases of overt thyroid dysfunction. However, opponents of universal thyroid screening argue that, asymptomatic borderline thyroid abnormalities such as subclinical hypothyroidism form the bulk of cases of thyroid dysfunction seen in pregnancy, and that there is a lack of high-quality evidence to support their screening and treatment. Due to the absence of strong evidence showing a benefit of levothyroxine therapy for subclinical hypothyroidism in pregnancy, confusion has arisen about the utility of screening using TSH during pregnancy. Therefore, well conducted large randomised trials with levothyroxine are still needed at early stage of pregnancy or preconception to refine the available information and settle this debate.

Those in favour argue that economic models have shown compared to high-risk screening; universal screening is cost effective even if only overt hypothyroidism was assumed to have adverse obstetric effects. As a result, several countries now implement universal screening. Also an increasing number of providers are performing universal screening, contrary to society guidelines. Furthermore, various prominent contributors to this field have argued that the limited evidence concerning the impact of untreated and treated subclinical disease has become a distraction from the core rationale for universal screening,

which is the beneficial impact of detecting and treating overt thyroid disease. They point out that the evidence supporting universal screening for overt disease stands independently from that of subclinical disease. It remains to be seen whether the views and independent practises of expert contributors to the society guidelines lead to change in guidelines in the near future in this important area.

References

1 - Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocrine reviews. 1997 Jun 1;18(3):404-33.

2- Ballabio M, Poshyachinda M, Ekins R. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. The Journal of Clinical Endocrinology & Metabolism. 1991 Oct 1;73(4):824-31.

3 - Alexander EK, Pearce EN, Brent GA et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid. 2017 Mar 1;27(3):315-89.

4 - Krassas GE, Poppe K, Glinoer D. Thyroid function and human reproductive health. Endocrine reviews. 2010 Oct 1;31(5):702-55.

5 - Cooper D, Laurberg P. Hyperthyroidism in pregnancy. The Lancet Diabetes & Endocrinology. 2013;1(3):238-249.

6 - Davis L, Lucas M, Hankins G, Roark M, Gary Cunningham F. Thyrotoxicosis complicating pregnancy. American Journal of Obstetrics and Gynecology. 1989;160(1):63-70.

7 - Millar LK, Wing DA, Leung AS, et al. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstetrics & Gynecology. 1994 Dec 1;84(6):946-9.

8 - Kriplani A, Buckshee K, Bhargava V, Takkar D, Ammini A. Maternal and perinatal outcome in thyrotoxicosis complicating pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1994;54(3):159-163.

9 - Taylor P, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus J, Dayan C et al. Global epidemiology of hyperthyroidism and hypothyroidism. Nature Reviews Endocrinology. 2018;14(5):301-316.

10 - Allan W, Haddow J, Palomaki G, Williams J, Mitchell M, Hermos R et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. Journal of Medical Screening. 2000;7(3):127-130.

11- Casey BM, Dashe JS, Wells CE, et al. Subclinical hypothyroidism and pregnancy outcomes. Obstetrics & Gynecology. 2005 Feb 1;105(2):239-45.

12- Allan WC, Haddow JE, Palomaki GE, et al. Maternal thyroid deficiency and pregnancy complications: implications for population screening. Journal of medical screening. 2000 Sep 1;7(3):127-30.

13 - Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and Subclinical Hypothyroidism Complicating Pregnancy. Thyroid. 2002;12(1):63-68.

14 - Wiles KS, Jarvis S, Nelson-Piercy C. Are we overtreating subclinical hypothyroidism in pregnancy? BMJ. 2015 Oct 12;351:h4726.

15 - Liu H, Shan Z, Li C, et al. Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study. Thyroid. 2014 Nov 1;24(11):1642-9.

16 - Stagnaro-Green A, Chen X, Bogden JD, Davies TF, Scholl TO. The thyroid and pregnancy: a novel risk factor for very preterm delivery. Thyroid. 2005 Apr 1;15(4):351-7.

17 - Breathnach FM, Donnelly J, Cooley SM, Geary M, Malone FD. Subclinical hypothyroidism as a risk factor for placental abruption: Evidence from a low-risk primigravid population. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2013 Dec;53(6):553-60.

18 - Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. The Journal of Clinical Endocrinology & Metabolism. 2010 Sep 1;95(9): E44-8.

19 - Lee SY, Cabral HJ, Aschengrau A, Pearce EN. Associations Between Maternal Thyroid Function in Pregnancy and Obstetric and Perinatal Outcomes. The Journal of Clinical Endocrinology & Metabolism. 2020 May;105(5):dgz275.

20 - Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. Thyroid. 2016 Apr 1;26(4):580-90.

21 - Abu BM. A Successful Model of Cancer Screening in Low Resource Settings: Findings of an Integrated Cancer Screening Camp from a Rural Setting of North India. Asian Pacific Journal of Cancer Care. 2020 Jun 7;5(2):83-6.

22 - Wilson JM, Jungner G. World Health Organization. Principles and practice of screening for disease.

23 - Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. New England Journal of Medicine. 1999 Aug 19;341(8):549-55.

24 - Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid. 2002 Jan 1;12(1):63-8.

25 - Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. The Journal of Clinical Endocrinology & Metabolism. 2010 Apr 1;95(4):1699-707.

26 - Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. New England Journal of Medicine. 2019 Apr 4;380(14):1316-25.

27 - Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. New England Journal of Medicine. 2012 Feb 9;366(6):493-501.

28 - Casey BM, Thom EA. Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. The New England Journal of Medicine. 2017 Aug 1;377(7):701-.

29 - Korevaar TI, Medici M, Visser TJ, Peeters RP. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nature Reviews Endocrinology. 2017 Oct;13(10):610-22.

30 - Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. European thyroid journal. 2014;3(2):76-94.

31 - Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. European thyroid journal. 2014;3(2):76-94.

32 - Vila L, Velasco I, González S, et al. Detection of thyroid dysfunction in pregnant women: universal screening is justified. Endocrinología y Nutrición (English Edition). 2012 Nov 1;59(9):547-60.

33 - Zhou Q, Acharya G, Zhang S, Wang Q, Shen H, Li X. A new perspective on universal preconception care in China. Acta obstetricia et gynecologica Scandinavica. 2016 Apr;95(4):377-81.

34 - Hubalewska-Dydejczyk A, Trofimiuk-Müldner M. The development of guidelines for management of thyroid diseases in pregnancy–current status. In Thyroid Research 2015 Dec (Vol. 8, No. 1, pp. 1-3). BioMed Central.