Thyroid dysfunction in pregnancy

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INTRODUCTION

Maternal thyroid state is an important predictor of pregnancy outcome. Both hyperthyroidism and hypothyroidism have been shown to have an adverse impact on pregnancy. There is a wide range in the prevalence of thyroid dysfunction worldwide. In the USA which is considered an iodine replete country, 2%-3% of apparently healthy, non pregnant women of childbearing age have an elevated serum TSH with the majority in the subclinical range1. In southern Iran, the prevalence of hypothyroidism among pregnant women was shown to be 13.7%3. In a study carried in India, the prevalence of thyroid dysfunction was high with subclinical hypothyroidism found in 6.47% and overt hypothyroidism found in 4.58% of pregnant women1. Hyperthyroidism is less commonly encountered in pregnancy with a prevalence of 0.2-0.6%2.

There is lack of data on the magnitude and different forms of thyroid dysfunction among pregnant women of Sri Lanka. Few studies have looked at the prevalence of iodine deficiency and autoimmune thyroid disease which are the two leading causes of hypothyroidism in pregnancy. In a cross sectional, nationally representative sample of pregnant women in Sri Lanka, median urinary iodine level was 113.7 μg/l, which was far below the WHO recommendation of a level between 150 and 249 μg/l, indicating inadequate iodine status of pregnant women in Sri Lanka. A study looking at the prevalence of thyroid autoantibodies in schoolgirls of Sri Lanka a decade ago, found the prevalence of thyroglobulin autoantibody (TgAb) to be markedly raised at 14.3% in 11 year olds and 69.7% among 16 year old girls2. Thyroid autoantibodies are known to be associated with thyroid dysfunction, mainly hypothyroidism. These observations raise the possibility of a high prevalence of thyroid dysfunction among pregnant women of Sri Lanka, which needs to be confirmed by studies.

CHANGES IN THYROID HOMEOSTASIS IN PREGNANCY

Transfer of thyroxine transplacentally, increased maternal renal clearance of iodine and changes in thyroid binding globulin disturb thyroid homeostasis in pregnancy. Thyroid hormone production which is iodine dependant gradually declines if the increase on iodine demand placed by the pregnant state, which averages 250 micrograms per day, is not met.

The reference range for serum thyroid stimulating hormone (TSH) and free thyroxine (FT4) are different during pregnancy, reflecting the physiological changes described above. The reference range for TSH is lower than outside pregnancy, while FT4 levels are highest in the first trimester due to the stimulatory effect of serum beta hCG on the TSH receptors. Until reference ranges are available for Sri Lankan women, the following reference range shown in box 1 could be adopted as normal for our pregnant women.

Symptoms of thyroid dysfunction are generally vague and non specific, and could easily be attributed to the physiological changes that occur in pregnancy. The clinical presentation of hyperthyroidism may not be obvious because symptoms of tachycardia, sweating, dyspnoea, and nervousness are seen in normal pregnancy. Generalised body aches, arthralgia, constipation and excessive sleepiness which are features of hypothyroidism too could be easily attributed to the hormonal changes of pregnancy. A high index of suspicion is therefore required for timely identification and appropriate treatment. Palpitations which are frequent and distressing, excessive sweating, increased bowel frequency, fine tremor of the outstretched hands, tachycardia and exaggerated deep tendon reflexes suggest thyrotoxicosis. Distressing arthralgia and myalgia, especially proximal myopathy, should prompt examination of the pulse rate for bradycardia and slow relaxing ankle jerks which are highly suggestive of hypothyroidism.

SCREENING FOR THYROID DYSFUNCTION IN PREGNANCY

At present, an aggressive case finding approach rather than universal screening is advocated for detection of thyroid dysfunction in pregnancy inspite of the significant impact thyroid dysfunction exerts on pregnancy. This is due to the Absence of consistent results on benefit of levothyroxine replacement in women

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Box 1- Reference range for thyroid function tests in pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Serum TSH (μIU/mL)</th>
<th>FT4 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>0.1-2.5</td>
<td>0.83-1.27</td>
</tr>
<tr>
<td>Second</td>
<td>0.2-3.0</td>
<td>0.71-1.05</td>
</tr>
<tr>
<td>Third</td>
<td>0.3-3.0</td>
<td>0.72-1.06</td>
</tr>
</tbody>
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with subclinical hypothyroidism, which forms the majority of thyroid dysfunction. However, a target case finding approach appears ineffective as the prevalence of SCH and overt hypothyroidism have found to be equal in targeted thyroid tested and untested women, while in another study testing only women in the high risk group was shown to miss a third of those with overt/subclinical hypothyroidism. The cost effectiveness of a universal screening program has also been demonstrated based on the assumption that treatment of SCH has an effect on IQ of the offspring, though studies are yet to confirm this. Until the results of such studies shed new light, a case finding approach is currently recommended.

All pregnant women should be assessed with serum TSH at the booking visit if any one of the features listed in Box 2 is found to be present. If TSH is abnormal (high or low) free T4 should be assessed.

THYROID DYSFUNCTION-HYPOTHYROIDISM

Worldwide, iodine deficiency is the commonest cause of hypothyroidism, while chronic autoimmune thyroiditis remains the leading cause in the developed world. Overt hypothyroidism is defined as an elevated serum TSH and low free T4 (FT4) or TSH> 10µIU/ml irrespective of the FT4 level. Miscarriage, preterm birth, gestational hypertension, low birth weight and fetal loss are known complications of maternal hypothyroidism. The fetus requires adequate thyroxine for central nervous system maturation in early gestation and is totally dependant on maternal thyroxine due to the inability of its thyroid gland to synthesize thyroxine until early second trimester. Maternal hypothyroidism is therefore associated with the much feared complication of neurodevelopmental delay in the offspring.

Subclinical hypothyroidism (SCH) defined as elevated TSH (based on trimester specific reference range) with normal free T4 level too appears to have an adverse impact on the pregnancy with increased incidence of miscarriage, gestational diabetes mellitus, gestational hypertension and pre eclampsia. The association between maternal SCH and impaired neuropsychological development in the offspring is less consistent than for overt hypothyroidism.

Levothyroxine is used to treat overt hypothyroidism. The benefits of levothyroxine therapy on subclinical hypothyroidism is less convincing with some studies failing to show a significant benefit in the absence of thyroid autoantibodies. A prospective randomized controlled trial by the National Institute of Child Health and Human Development – USA and similar studies which are underway, will hopefully enlighten us this area in the near future. Given the fact that levothyroxine is relatively cheap and devoid of significant side effects, most authorities incline towards prescribing levothyroxine for SCH even in the absence of thyroid autoantibodies. Isolated hypothyroxinaemia (normal TSH with low FT4) does not need to be treated.

The aim of treatment should be maintenance of TSH within the trimester specific reference range. Serum TSH is adequate for monitoring maternal thyroid status and should be assessed every 4 weeks during pregnancy.

In women with pre existing hypothyroidism contemplating pregnancy, periconceptional care should ensure that TSH is maintained within the reference range for the first trimester (ie TSH < 2.5 µIU/ml). It also important to increase chances of conception as infertility is known to be associated with SCH. In case of unplanned pregnancy, the dose of thyroxine should be increased by 25-30% of the preconception dosage as early as possible while awaiting the result of TSH. In all other women seen at any other time in pregnancy, a TSH should be performed as soon as possible and maintained within the trimester specific reference range. In a woman newly diagnosed to have overt hypothyroidism, the usual starting dose of thyroxine is 2µg/Kg/d (maximum of 2.5 µg/kg/d). TSH performed at 4 weeks should help in titrating the dose thereafter.

The woman should be advised on general measures that enhance the

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**Box 2- Clinical features that require thyroid assessment in pregnancy**

- A family history of autoimmune thyroid disease, hypothyroidism or hyperthyroidism
- Presence of a goitre
- Presence of thyroid antibodies, primarily thyroid peroxidase antibodies (TPOAb)
- Symptoms or clinical signs suggestive of hypothyroidism or hyperthyroidism
- Women with type 1 diabetes mellitus, or other autoimmune disorders
- Women with a history of infertility
- Women with a prior history of miscarriage or preterm delivery
- Women with prior therapeutic head or neck irradiation or prior thyroid surgery
- Women currently receiving Levothyroxine replacement
- Women living in a region presumed to be iodine deficient
absorption of thyroxine. Taking thyroxine on an empty stomach upon waking in the morning with a lapse of at least half an hour until a drink or meal and avoiding taking iron and calcium supplements concomitantly should be advised upon.

Thyroxine is safe during breast feeding. Women with pre existing hypothyroidism could be maintained on their pre pregnancy dose of thyroxine with serum TSH reviewed at 6 weeks postpartum. Neonatal TSH should be tested within the first week.

THYROID DYSFUNCTION-HYPERTHYROIDISM

‘Transient thyrotoxicosis of pregnancy’ occur due to the stimulatory effect of serum β hCG on the TSH receptor and the commonest cause of thyrotoxicosis in pregnancy which is known to affect 1-3% of pregnancies. Graves disease remains the commonest pathological cause of maternal hyperthyroidism in pregnancy. Complications of maternal hyperthyroidism include miscarriage, gestational hypertension, preterm birth, fetal growth restriction, stillbirth, low birth weight, thyroid storm, and maternal congestive heart failure. High levels of maternal thyroid receptor stimulating antibodies (TRAb) which characterises Graves disease, is associated with an increased risk of fetal/neonatal thyrotoxicosis, which although transient can cause significant morbidity.

Overt hyperthyroidism is characterised by depressed serum TSH and high levels of free T4. Overt hyperthyroidism can be treated though there is a lack of evidence of benefit in treatment of subclinical hyperthyroidism (depressed TSH levels with normal FT4) or isolated hyperthyroxinaemia (normal levels of TSH with elevated FT4) in pregnancy. Antithyroid drugs are the mainstay of management of maternal hyperthyroidism. Propylthiouracil should be used in the first trimester of pregnancy due to lesser risk of teratogenicity while Carbimazole may be commenced from the second trimester onwards. This will reduce the risk of liver toxicity associated with prolonged use of Propylthiouracil.

The usual starting dose for Propylthiouracil is 100-300mg daily in divided doses and for Carbimazole it is 10-15mg daily in divided doses. Antithyroid drugs have no place in managing thyrotoxicosis associated with hyperemesis gravidarum, though beta blockers could be used if troublesome hypermetabolic symptoms are present.

The aim of treatment in thyrotoxicosis is to maintain FT4 in the upper normal range using the smallest dose of antithyroid drug. This reduces the risk of fetal hypothyroidism. Beta adrenergic blocking agents (Eg Propranolol 20-40 mg 6 hourly ) may be used for controlling troublesome hypermetabolic symptoms such as palpitations and tremulousness, with the dose reduced as early as possible in view of risk of fetal growth restriction, fetal bradycardia and neonatal hypoglycaemia. In the vast majority of cases, beta blockers could be discontinued in 1-2 weeks.

Thyroidecotmy is rarely indicated to control hyperthyroidism and if required, is usually performed in the second trimester. Radioactive iodine is contraindicated during pregnancy. A woman with pre-existing hyperthyroidism, should be rendered euthyroid before attempting pregnancy with TSH maintained within the reference range for the first trimester. If radioactive iodine has been used to achieve euthyroidism, conception should be delayed for a minimum of 6 months.

Women with Graves disease may experience disease flares in the first trimester, though a gradual improvement is expected as pregnancy advances. Discontinuation of all antithyroid therapy is feasible in 20%-30% of patients in the third trimester. The exceptions are women with high levels of thyroid receptor stimulating antibodies (TRAb), in whom it is needed to be continued until delivery. Maternal serum TRAb levels should be determined between 24 to 28 weeks in women with active hyperthyroidism, those with a history of thyroidecotomy for treatment of hyperthyroidism, those treated with radioactive and in women who have had an infant with hyperthyroidism.

Fetal wellbeing could be affected in the presence of elevated TRAb and in poorly controlled hyperthyroidism. Ultrascanography appearance of fetal tachycardia (>170 bpm, persistent for over 10 minutes), fetal growth restriction, fetal goiter, accelerated bone maturation, signs of congestive heart failure, and fetal hydrops may suggest potential underlying fetal hyperthyroidism.

American thyroid association recommends to offer serial fetal wellbeing assessment in women who have uncontrolled hyperthyroidism and/or women with high TRAb levels (greater than three times the upper limit of normal). These women should be managed under a maternal-fetal medicine specialist and monitoring should include ultrasound for heart rate, growth, amniotic fluid volume, and fetal goiter.

POSTPARTUM THYROID DYSFUNCTION

Autoimmune thyroiditis is characterised by thyroid inflammation caused by autoantibodies. Thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TgAb) are the two most important autoantibodies described. These antibodies when present in high titres could cause a destructive thyroiditis which classically results in hyperthyroidism due to release of preformed hormones followed by hypothyroidism due to exhaustion of thyroid reserve and finally euthyroidism. In the western world, 10-20% of pregnant euthyroid women were found to have thyroid autoantibodies in first trimester. There is a growing body of evidence linking adverse pregnancy outcomes with autoimmune thyroiditis even in the absence of thyroid dysfunction. Development of overt or subclinical hypothyroidism, miscarriage, preterm delivery, placental abruption, postpartum depression and reduced IQ in the offspring are some of the adverse associations described. In the only prospective interventional trial to date, levothyroxine replacement in TPOAb positive women has shown to significantly reduce the rate of...
Downregulation of the maternal immune system is pertinent for fetal survival. The maternal immune system which is suppressed during pregnancy, rebounds back to normalacy in the postpartum period. It has been shown that autoantibodies seen in women in the first trimester gradually wane due to the immune tolerance of pregnancy and increase in the postpartum period, at times overshooting the normal level. This autoimmune process could lead to preterm delivery. The incidence of PPTD ranges from 4%-9%. It is characterised by elevated thyroid peroxidase (TPOAb) and/or thyroglobulin antibodies (TgAb) and is the result of an autoimmune destructive process that lies relatively quiescent in the antenatal period. There is lymphocytic infiltration of the thyroid gland and hypoechoigenicity of the gland on ultrasound scanning. PPTD has been shown to occur in as much as 33-50% of women with positive TPO Ab detected in the first trimester.

The classical course of PPTD is a thyrotoxic phase which occurs around 1-4 months following delivery, followed by a hypothyroid state around 4-8 months and finally a state of euthyroidism. A hyperthyroid phase followed by return to normalacy and a hypothyroid phase alone are also identified. Although clinical and biochemical abnormalities are transient in the majority, 20-30% of women will remain permanently euthyroid.

### Figure 1 – Management of postpartum thyroid dysfunction

**Hyperthyroidism**
- If symptomatic
  - Treat with propranolol
  - No place for ATD

**Hypothyroidism**
- Asymptomatic
  - Do not treat
  - Monitor thyroid functions 6 weekly

**Euthyroid**
- See if
  - Symptomatic
    - TSH >10 µIU/mL
    - Breast feeding
    - Attempting pregnancy and TSH >2.5-10 µIU/mL

**Repeat TSH every 2 months until 1 year postpartum**
- **If none of the above present**
  - Do not treat
- **If any of the above present**
  - Start treatment

**Yearly TSH measurement in women who had PPTD and returned to the euthyroid state**
- **• Continue treatment until 6-12 months**
- **• Attempt weaning by halving the dose and repeating TSH in 6-8 weeks**
- **• Do not attempt weaning if patient is pregnant, breast feeding, or attempting to conceive**
hypothyroid at one year postpartum while long term follow up studies reveal that nearly 50% of those whose thyroid function recovers after an episode of PPTD will become hypothyroid at seven years. PPTD which is a treatable condition causes significant maternal morbidity in the new mother but often goes unrecognised as the symptoms are blamed on maternal depression or anxiety that are known to occur following childbirth.

Certain risk factors have been identified for the development of PPTD. A history of autoimmune thyroid illness, other autoimmune disease and history of PPTD are some of these. Identification of risk factors for PPTD should lead to screening with serum TSH and timely intervention, while routine monitoring thereafter will enable early identification of permanent hypothyroidism. (Figure 1)

Thyroid dysfunction exerts a major impact on the mother, fetus, neonate and child. Inspite of evidence of significant disease burden, there is currently no rigorous screening program to detect thyroid dysfunction in pregnancy and postpartum period in Sri Lanka. One major reason behind this is inadequate awareness on the magnitude and forms of thyroid dysfunction in pregnant women in Sri Lanka due to paucity of data, which needs to be addressed immediately.

REFERENCES