Thyroid Disorders in Pregnancy

Samar Banerjee

Introduction

Over the past several years it has been proved that maternal thyroid disorder influence the outcome of mother and fetus, during and also after pregnancy. The most frequent thyroid disorder in pregnancy is maternal hypothyroidism. It is associated with fetal loss, placental abruptions, pre-eclampsia, preterm delivery and reduced intellectual function in the offspring. In pregnancy, overt hypothyroidism is seen in 0.2% cases and sub clinical hypothyroidism in 2.3% cases. Fetal loss, fetal growth restriction, pre-eclampsia and preterm delivery are the usual complications of overt hyperthyroidism (low TSH and high T3, T4) seen in 2 of 1000 pregnancies whereas mild or sub clinical hyperthyroidism (suppressed TSH alone) is seen in 1.7% of pregnancies and not associated with adverse outcomes. Autoimmune positive euthyroid pregnancy shows doubling of incidence of miscarriage and preterm delivery. Worldwide more than 20 million people develop neurological sequel due to intra uterine, iodine deprivation. Other problems of thyroid disorders in pregnancy are post partum thyroiditis, thyroid nodules and cancer, hyper emesis gravidarum etc. Debates and disputes persist regarding several protocol and management plan in this specific spectrum of diseases. An attempt is made hereby to formulate an acceptable and applicable guideline in the scenario of country, based on evidences and background knowledge.

Physiology of Thyroid in Pregnancy

Thyroid hormones consist of thyroxin (T4) and triiodothyronine (T3) of which active forms are the free portions (fT3, fT4) consisting of 1% of total hormones. The fT3 fraction is biologically more significant and derived from conversion of fT4 at liver, kidney and muscle. The fT4 hormone acts through specific nuclear receptors of fT3, situated in most of the tissues. TSH secreted from anterior pituitary act as negative feedback from fT3 levels. Dietary iodine is essential for this thyroid hormone synthesis.

Fetal aspects

In pregnancy, fetus receives iodine from maternal source in all the trimesters. Fetus receives thyroxin from mother up to 12 weeks through placental circulation but not TSH or fT3. Thyroxin is partially converted to fT3 and combines with receptors in fetal brain and responsible for fetal brain development. From 12th week, placental changes resist T4 passage to fetus and fetal pituitary thyroid axis start functioning like adult.

Maternal aspects

1. In pregnancy, half life of Thyroxin Binding Globulin (TBG) increases from 15min to 3days and concentration becomes 3 times by 20weeks due to the effect of oestrogen driven glycosylation, which increases the level of T3 and T4 making its estimation non reliable. But fT3 and fT4 remain unaffected, and are of choice for estimating the thyroid function during pregnancy.

2. HCG and TSH due to structural similarity produce hormone spillover syndrome in 1st trimester, manifested as stimulation of TSH receptors by HCG and biochemical hyperthyroidism. This is common in multiple pregnancy, hyper emesis gravidarum and trophoblastic diseases. Diagnosis of false hyperthyroidism should be avoided in these cases.

3. Depletion of iodine can occur due to increased glomerular filtration and greater thyroidal uptake due to higher T4 concentration. In several maternal iodine deficiency, compensation if fails can lead to cretinism in the offspring.

4. Concentration of the enzyme deiodinase III (which converts T4 to T3 and further breakdown) is increased in placenta and reduces thyroxin transfer.

About 2 to 5% of pregnant woman suffer from any variety of thyroid disorders and timely intervention can be done if detected early. Because of physiological changes values of thyroid hormones during pregnancy differ from non-pregnant values. Values in pregnancy also vary from trimester to trimester and no consensus about this value has been made yet. Coutez C et al., established the following value as shown in table 1.

In 2008, Marwaha RK et al, first time presented the trimester specific thyroid function values in Indian Woman. These are shown in table 2.

Table 1: Median values of trimester specific thyroid hormones (rounded to nearest 0.5)

<table>
<thead>
<tr>
<th>Reference range used for non-pregnant population</th>
<th>1st Trimesters</th>
<th>2nd Trimesters</th>
<th>3rd Trimesters</th>
</tr>
</thead>
<tbody>
<tr>
<td>fT4 (pmol/L) 9 – 26</td>
<td>10 -16</td>
<td>9 – 15.5</td>
<td>8 -14.5</td>
</tr>
<tr>
<td>fT3 (pmol/L) 2.60 - 5.7</td>
<td>3-7</td>
<td>3 – 5.5</td>
<td>2.5 – 5.5</td>
</tr>
<tr>
<td>TSH (mu/L) 0.3 - 4.2</td>
<td>0.5-5.5</td>
<td>0.5 - 3.5</td>
<td>0.5- 4</td>
</tr>
</tbody>
</table>

Table 2: Trimester wise median values of thyroid hormones in Indian women

<table>
<thead>
<tr>
<th>Reference range used for non-pregnant population</th>
<th>1st Trimesters</th>
<th>2nd Trimesters</th>
<th>3rd Trimesters</th>
</tr>
</thead>
<tbody>
<tr>
<td>fT4 (pmol/L) 3.7 – 7.2</td>
<td>0.37 – 6.58</td>
<td>2.7 – 7.69</td>
<td>2.93 – 5.92</td>
</tr>
<tr>
<td>fT3 (pmol/L) 12.0 – 23</td>
<td>8.04 – 22</td>
<td>9.26 – 22.12</td>
<td>9.54 – 27.02</td>
</tr>
<tr>
<td>TSH (mu/L) 0.27 – 42</td>
<td>0.04 – 10.8</td>
<td>0.026 – 10.85</td>
<td>0.2 – 9.55</td>
</tr>
</tbody>
</table>

Professor, Department of Medicine, Vivekananda Institute of Medical Sciences, Kolkata; Ex Professor and Head Department of Medicine, In-Charge, Diabetic Clinic, N.R.S. Medical College, Kolkata
would only screen the high group woman who should be tested definitively are the following.11

Screening of pregnant women

1. History of hypothyroidism or thyroid lobectomy
2. Family history of thyroiditis
3. Goiter
4. Thyroid auto-antibodies
5. Symptoms, signs or biochemical markers suggestive of thyroid disease
6. Type 1 diabetes
7. Other autoimmune disorders
8. Infertility
9. Previous head or neck irradiation
10. History of miscarriage or preterm delivery

Routine screening in pregnancy and neonates

The problem of thyroid disease in pregnancy is receiving increasing attention from many scientific concerns. Thyroid function in pregnancy is characterized by a T4 surge at 12 weeks which declines subsequently. There is a fall in the serum thyroid hormone concentrations in the second half of pregnancy. However, data shows that some women may have thyroid hormone levels within reference ranges even in the second half of pregnancy. Development of the fetal brain is dependent on T4 transportation to the fetus, which eventually depends upon adequate maternal iodine supply. There is current concern that adequate iodisation is not present in large parts of India and other countries. A growing amount of evidence suggests that thyroid autoimmunity is associated with fetal loss, however, the mechanism remains unclear and carefully conducted studies are required to elucidate optimal therapy. The incidence of hyperthyroidism in pregnancy is uncommon, but effects on both mother and child are critical if untreated. Substantial evidence also exists which shows that low maternal thyroid hormone levels for free T4 in the upper nonpregnant reference range.

Maternal hypothyroidism

1. If a below normal serum TSH level is detected, hypothyroidism must be distinguished from both normal physiology during pregnancy and hyperemesis gravidarum. Presence of autoimmunity, a goiter, and TRAb can differentiate Graves’ disease from gestational thyrotoxicosis.

2. In cases of hypothyroidism diagnosed before pregnancy, adjust the preconception T4 dose to reach a TSH level not higher than 2.5μIU/ml before pregnancy.

3. By 4-6 weeks of gestation, the T4 dosage needs to be increased by about 30-50%.

4. If overt hypothyroidism is diagnosed during pregnancy, thyroid function should be normalized as rapidly as possible. The target is to achieve and maintain TSH concentrations below 2.5μIU/ml in the first trimester (or 3μIU/ml in the second and third trimesters) or to trimester-specific normal TSH ranges. This can be achieved by rapidly titrating the T4 dosage to reach and maintain the target TSH levels. A reassessment of the thyroid function should be carried out within 30 to 40 days.

5. Women who have thyroid antibodies in the early stages of their pregnancy but are otherwise euthyroid, should be monitored for elevations of TSH above the normal range because they are risk of developing hypothyroidism.

6. Subclinical hypothyroidism: Recommend T4 replacement as T4 treatment has been shown to improve obstetrical outcome, though do not modify long-term neurological development in the offspring.

7. After delivery, dose of T4 need to be decreased in most hypothyroid women.11

Guideline for Treatment of Thyroid Disorders

Hypothyroidism and pregnancy

1. Both maternal and fetal hypothyroidism exert serious adverse effects on the fetus, so maternal hypothyroidism should be avoided by early diagnosis at the first prenatal visit or at diagnosis of pregnancy.
Women who have a negative TRAb and do not require ATD have a very low risk of fetal or neonatal thyroid dysfunction.

7. Iodine should be avoided in a woman who is or may be pregnant. Iodine should not be used in a pregnant woman. However, on inadvertent use, the patient should be promptly informed about the danger of radiation to the fetus and about thyroid destruction if the patient has been treated after the 12th week of gestation. There are no data for or against recommending termination of pregnancy after iodine exposure.

8. Pregnant women with TRAb or those treated with ATD should have a fetal ultrasound to detect fetal thyroid dysfunction. This may include growth restriction, hydrops, presence of goiter, and cardiac failure.

9. Evaluate newborns of mothers with Graves’ disease for thyroid dysfunction and treated if indicated.

Gestational hyperemesis and hyperthyroidism

1. Measure Thyroid function tests in all patients with hyperemesis gravidarum

2. ATD treatment to be given to overt hyperthyroidism due to coincident Graves’ disease and few women with hyperemesis gravidarum

Autoimmune and thyroid disease and miscarriage

Universal screening for anti thyroid antibodies and possible treatment cannot be recommended as there are very few reports regarding positive association between the presence of thyroid antibodies and pregnancy loss.

Thyroid nodules and cancer

1. Fine-needle aspiration (FNA) cytology, preferably Ultrasound-guided should be advised if thyroid nodules larger than 1 cm are detected in pregnancy.

2. Pregnancy should not be interrupted and surgery should be offered in the second trimester before fetal viability when nodules discovered in the first or early second trimester are malignant. Women found to have cytology indicative of papillary cancer or follicular neoplasm without evidence of advanced disease and who prefer to wait until the delivery, they that can be counseled that most well differentiated thyroid cancers are slow growing and surgical treatment soon after delivery is unlikely to adversely affect prognosis.

3. In pregnant women with a previously treated thyroid cancer, a positive FNA for cancer or suspicion of cancer, and those who elect to delay surgery until postpartum, treatment with thyroid hormone to achieve suppressed but detectable TSH is advisable.

4. Iodine should not be given to lactating women. Pregnancy should be avoided for 6 months to 1 yr in them.

Iodine nutrition during pregnancy

Increase daily iodine intake to 250 µg on average during pregnancy and breastfeeding by encouraging the use of iodized salt.

Postpartum thyroiditis (PPT)

1. TSH estimation at 3 and 6 months in women known to be thyroid peroxidase antibody positive, for women with type 1 diabetes mellitus (PPT 3-fold greater).

2. Women with a history of PPT have a markedly heightened risk of developing permanent primary hypothyroidism within 5 to 10 years, should undergo annual TSH assessments.

3. Asymptomatic women with PPT who have a TSH above the reference range but less than 10 µU/ml and who are not planning a subsequent pregnancy do not necessarily require intervention but should, if untreated, be re-monitored in 4–8 weeks. Symptomatic women and women with a TSH above normal and who are attempting pregnancy should be treated with levothyroxine.

4. Women with postpartum depression should be screened for hypothyroidism and appropriately treated

Conclusions

- Uncontrolled or inadequate control of thyroid dysfunction in pregnancy is associated with adverse fetal and maternal outcomes
- Hyperthyroidism in pregnancy requires careful control of maternal disease whilst avoiding fetal hypothyroidism
- Propylthiouracil is the preferred antithyroid drug in pregnancy although methimazole can be used where propylthiouracil is unavailable
- Synthetic levothyroxine is the treatment of choice in hypothyroidism
- Patients with pre-existing hypothyroidism usually require an increase in thyroxine dose in pregnancy
- Most patients with postpartum thyroiditis will require treatment during the hypothyroid phase
- Long-term follow-up of patients with this syndrome is essential owing to the risk of permanent hypothyroidism
- Subclinical hypothyroidism in pregnancy requires replacement treatment
- Excellent maternal and fetal outcomes can be achieved with appropriate management of thyroid dysfunction in pregnancy.

References