Hypothyroidism in pregnancy – consensus on testing and treatment

Abstract

Maternal hypothyroidism is relatively common but frequently undiagnosed in pregnancy. The consequences on mother and fetus are detrimental. The guidelines by ATA present a lucid explanation for diagnosis and treatment of this ailment but it has to be seen and interpreted in context to local regional demographics of population. The present paper is based on studies in literature and ATA guidelines for treatment of hypothyroidism in pregnancy.

Keywords: Maternal hypothyroidism, Thyroid, Pregnancy

Introduction

Pregnancy affects thyroid physiology resulting in: increase in size (10-30%), increase production of thyroid hormones like thyroxine (T4) & Triiodothyronine (T3) by 50% and increase in daily Iodine requirement of Iodine by roughly 50%, to the non pregnant state in woman. The physiological changes in thyroid are sine qua non of pregnancy but the pathological process may result in thyroid disease. One of the problematic areas in diagnostics is interpretation of thyroid function tests in pregnant woman as it differs from non pregnant state. The accurate upper reference interval of serum TSH in pregnant woman is not clearly defined because of the stimulation of thyroid hormone secretion by placental human chorionic gonadotropin (hCG) resulting in decreased maternal thyrotrpin concentration and thyroid peroxidase (TPOAb) or thyroglobulin antibody (TgAb) positivity that adversely impacts maternal thyroid status. Physiological changes in pregnancy cause increased renal iodine excretion, increased thyroid hormone production, increase in thyroid binding proteins and stimulation of thyroid by placental beta hCG. Thyroxine binding globulin (TBG) and total T4 (TT4) are increased in pregnancy by 7 weeks of gestation, attain peak concentration by 16 weeks and there after remain high till delivery causing reduction in serum TSH concentration. These cutoffs were based on studies comprising a total cohort of about 3000 pregnant women. Increase in Serum TSH level with decreased Serum FT4 concentration during pregnancy is hallmark of primary maternal hypothyroidism. The literature studies also mention that this biochemical profile is seen in healthy non pregnant women. One of the factor responsible for high TSH in non pregnant women is iodine deficiency. In that case where iodine levels are within normal range the causative etiology of hypothyroidism is autoimmune thyroid disease. This further complicates the situation in pregnancy as high TSH levels in pregnancy are associated with detection of thyroid antibodies in 30-60% of cases. In the 2011 American Thyroid association (ATA) guidelines, the upper reference limit for serum TSH is 2.5mU/L in the first trimester and 3.0mU/L in the second and third trimester respectively. These cutoffs were based on studies comprising a total cohort of about 5500 subjects. The consensus on reference intervals continues as evidenced by other studies. Mother and fetal complications are widely. The various kit manufacturers emphasize on establishment of reference intervals by laboratories themselves but it is often impractical for laboratories to recruit subjects and perform the herculean task. The laboratories on the other hand adopt pregnancy related reference ranges as provided by the manufacturers of test kits which unfortunately lack adjustments as per race, ethnicity and population specific iodine uptake, all these add to uncertainty of FT4 estimate making reliance on FT4 test during pregnancy questionable. The TT4 and calculated FT4 show inverse relation with TSH in nutshell TT4 measurement is superior to immunoassay measurement of FT4. FT4 should be measured by liquid chromatography (LC) or mass spectroscopy (MS) as they are at par with measurement by classical equilibrium dialysis method. Unfortunately LC and or MS are not used by laboratories due to high instrument and operational costs. Calculated FT4 index can reliably be done using TT4 concentration and clinically acceptable upper reference range is determined by shifting the non pregnant limit 50% higher. However, this is applicable after 16 weeks of pregnancy. Estimation of FT4 before 16 weeks can be made by increasing the upper limit of non pregnant reference limit by 5% per week of pregnancy beginning with 7th week.

Defining maternal hypothyroidism

Increase in Serum TSH level with decreased Serum FT4 concentration during pregnancy is hallmark of primary maternal hypothyroidism. The literature studies also mention that this biochemical profile is seen in healthy non pregnant women. One of the factor responsible for high TSH in non pregnant women is iodine deficiency. In that case where iodine levels are within normal range the causative etiology of hypothyroidism is autoimmune thyroid disease. This further complicates the situation in pregnancy as high TSH levels in pregnancy are associated with detection of thyroid antibodies in 30-60% of cases. In the 2011 American Thyroid association (ATA) guidelines, the upper reference limit for serum TSH concentration during pregnancy was defined as 2.5mU/L in the first trimester and 3.0mU/L in the second and third trimester respectively. These cutoffs were based on studies comprising a total cohort of about 5500 subjects. The consensus on reference intervals continues as evidenced by other studies. Mother and fetal complications are

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higher in TPOAb positive pregnant women for unknown causes. Therefore, it is difficult to set a cut off of maternal TSH level for therapy related decision making.

**Pregnancy specific TSH reference range**

a. Who should define- Laboratory itself

b. Population selection- Healthy pregnant woman with adequate iodine uptake

The upper limit of TSH is 4.0mU/L which for most assays is nearly equal to reduction of non pregnant reference range by 0.5mU/L. It is also suggested to screen all pregnant women for TPOAb status when TSH is above 2.5mU/L.

**Adverse outcome**

Maternal hypothyroidism results in adverse pregnancy related complications ranging from premature & low birth weight, loss of pregnancy, poor fetal neurocognitive development, lower IQ of new born. Different studies have found maternal and child complications due to maternal hypothyroidism like Abalovich et al. - fetal loss in 60% of subjects and Leung et al. - gestational hypertension in 22% patients. The association of pregnancy loss with maternal hypothyroidism was seen in studies by Negro et al., Benhadi et al. and Liu et al. Pregnancy loss is difficult to determine as many pregnancies occur before they are recognized. In study by Negro et al, higher incidence of pregnancy loss was noted in woman with TSH level >2.5mU/L is compared to those with TSH levels <2.5mU/L. The TPO Ab positivity had adverse effect on pregnancy even in situations where maternal TSH was within trimester specific normal range. Casey et al. in a large study of 17,298 pregnant woman found that the risk of premature delivery was not consistent as the increased risk of premature delivery at <34 weeks was 4% (p=0.01) in compared to <32 weeks 2.5% (p=0.01) and <36 weeks 7% (p=0.39). Similar adverse Pregnancy related outcomes were observed in meta analysis which have shown that TPOAb positivity in pregnant woman exacerbates pregnancy related complications.

The effect of maternal hypothyroidism on neurocognitive development of fetus is still unclear. Conflicting literature studies make things more difficult for clinicians in deciding treatment of maternal hypothyroidism solely to prevent fetal cognitive lag. Some studies showed reduction of IQ of children born to hypothyroid woman whereas others show no effect of subclinical hypothyroidism on motor skills and language development by comparing treatment and placebo. In these studies LT4 treatment was commenced after completion of I trimester whereas when treatment was started early as in animal studies significant impact on neuro cognitive milestones was noted. The conflicting literature reports are attributed to the fact that over past century iodine supplementation has been stressed by various countries and severe iodine deficiency is less commonly encountered rather Hashimoto’s thyroiditis takes the driver’s seat as etiology of maternal hypothyroidism. Study of Po et al. reported decreased psychomotor test scores with below normal FT4 levels in presence of normal serum TSH levels in woman. Li et al. and other studies observed low IQ, delay in language and poor motor function in children born to hypothyroid mothers. However there are limited studies in literature to show that LT4 administration improves or reduces harmful effects of maternal hypothyroidism on fetus. In a recent study by Korevaar et al. it was found that both low and high FT4 levels were associated with lower IQ of child and there was reduced cerebral gray matter volume in brain as assessed by MRI.

**Treatment**

The detrimental effects of maternal hypothyroidism have been shown in various studies leading to adverse outcome in pregnancy. There is lack of randomized control trial (RCT) to show occurrence of pregnancy loss in hypothyroid patients. A RCT demonstrated improved pregnancy related outcome in woman treated with LT4 since I trimester. In other studies, lower pregnancy loss was observed when TPO Ab positive woman who were biochemically euthyroid were treated with LT4. There is paucity of literature on trials involving TPOAb Negative woman. The current recommendation suggests that woman with elevated TSH should in addition undergo TPOAb status evaluation. A daily dose of 50ug/day is required for treatment of hypothyroidism.

**LT4 therapy indications:**

a. TPOAb positive with TSH greater than pregnancy specific reference range

b. TPOAb positive with TSH greater than 2.5mU/L or age specific reference range and lower than upper limit of pregnancy specific range

c. TPOAb Negative with TSH more than 10Mu/L

LT4 therapy is not indicated for TPOAb negative woman with normal trimester specific TSH and for isolated Hypothyroxinemia. Oral LT4 therapy is recommended and T3 or desiccated thyroid should not be used. It is worth emphasizing that it is T4 that is required for developing fetal brain. The majority of fetal T3 is derived from maternal T4 as fetal CNC is impermeable to T3 containing preparation should be avoided during pregnancy. The target of treatment is to keep TSH below lower half of trimester specific reference range or in its absence below 2.5mU/L. Glinoer et al. found that there is increased requirement of T4 during gestation and therefore TPOAb positive euthyroid woman might develop sub clinical hypothyroidism in later pregnancy.

Woman who have hypothyroid (treated or untreated), or post hemithyroidectomy or received radioactive iodine should undergo TSH measurements every 4 weeks till mid gestation and at least once at 30 weeks. Hypothyroid women planning or suspected or confirmed for pregnancy should increase the dose of LT4 by 20-30% and inform physician for testing and evaluation. Patient should gradually taper off to preconceptional time dosing. A repeat thyroid function test is recommended at 6 weeks post partum while for those withinLT4<50ug/Da discontinuation is followed by TSH evaluation at 6 weeks is suggested.

**Conclusion**

Maternal hypothyroidism is relatively common but frequently undiagnosed in pregnancy. The consequences on mother and fetus are detrimental. The guidelines by ATA present a lucid explanation for diagnosis and treatment of this ailment but it has to be seen and interpreted in context to local regional demographics of population.

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None.
Conflicts of interest

The author declares that there is no conflict of interest.

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Endocrinology and metabolism in pregnancy – consensus on testing and treatment

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