Guest Editorial 1

Thyroid and Pregnancy: A Systematic Review

ABSTRACT

Pregnancy acts, like a stress test for the thyroid gland and results in hypothyroidism in women who are iodine deficient or have limited thyroid reserve, and postpartum thyroiditis in previously euthyroid women with underlying Hashimoto's thyroiditis. However, there is inconclusive evidence to recommend for or against the universal serum TSH screening at the 1st trimester visit of a pregnant woman and trimester specific cut-off values should be used for monitoring the thyroid function (whenever performed). Nonspecific complaints, like irritability or anxiety in a postpartum lady should be investigated to rule out postpartum thyroiditis and not merely considered as maladjustment on the part of the lady. Thyroid nodules can grow in size during pregnancy but usually are well tolerated and can be operated postpartum. If deemed necessary during pregnancy, surgery should be carried out in the 2nd trimester for the same.

Keywords: Anti-TPO antibodies, L-thyroxine, Pregnancy, TSH.

INTRODUCTION

Pregnancy impacts the functioning of the thyroid gland profoundly and is associated with a 10 to 40% increase in the size of the gland (iodine-replete areas show greater increase), 50% increase in the production of T4 and T3 along with a 50% increase in the daily requirement of iodine. These physiological changes can render a pregnant, iodine-deficient, euthyroid woman in the 1st trimester, hypothyroid during the later stages of pregnancy.

Human chorionic gonadotropin (hCG), secreted by the placenta, also impacts thyroid function as it simulates TSH activity *in vivo*, thereby suppressing its secretion.[1,2] Evidence suggests that throughout pregnancy, the TSH values are lower than the prepregnant state, and may even be below the classical lower limit of 0.4 mIU/L.[3,4] Human chorionic gonadotropin concentrations are increased to a greater extent in multiple pregnancies, therefore, the downward shift is even more significant in them. Since the levels of hCG decrease as the pregnancy increases, those of TSH follow the reverse trend. Therefore, trimester specific cut-off values of TSH should be used for diagnosing hyper- or hypothyroidism during pregnancy (and not the usual ones for nonpregnant individuals). The recommended reference ranges are: 1st trimester—0.1 to 2.5 mIU/l, 2nd trimester—0.2 to 3.0 mIU/l and 3rd trimester—0.3 to 3.0 mIU/L5.

Studies also report a significant decrease in the fT4 levels with the progression of pregnancy.[3,6,7] Its measurements are complicated by the increased levels of thyroid binding globulin (TBG) and decreased levels of albumin during pregnancy, which make the immunoassays unreliable.[8,9] The best method to assess fT4 during pregnancy is to measure T4 in the dialysate/ultrafiltrate of the serum samples employing online extraction/liquid chromatography or tandem mass spectrometry.[5] However, if these are unavailable, the clinician can use whichever method is available, with the knowledge of its shortcomings. It must be emphasized here that serum TSH is a superior indicator of thyroid function in pregnancy.[5]

Primary maternal hypothyroidism is defined as the increase in serum TSH levels during pregnancy. Depending upon the fT4 levels, it is further classified as Overt (OH-fT4 levels decreased) or subclinical (SCH-normal fT4 levels). This distinction is important, as studies show a more consistent relationship between adverse maternal and fetal outcomes and OH than SCH. Overt hypothyroidism is associated with an increased risk of premature birth, low birth weight and miscarriage. Some studies found a 22% increase in the risk of gestational hypertension[13] while others have found detrimental effects on neurocognitive development of the fetus.[14] Subclinical hyperthyroidism can also be associated with similar adverse effects but the data regarding the same are inconclusive.[10] Thus, all patients found to have OH should be treated with oral L-thyroxine (other preparations are not recommended). The decision whether to treat SCH remains debatable. Both OH and SCH patients should be followed up with serum TSH levels every 4 weeks upto 16 to 20 weeks period of gestation and then at least once between 26 to 32 weeks.

Euthyroid women (not receiving L-thyroxine) who are thyroid autoantibody positive (TAb+) also require the same monitoring during pregnancy as they have increased propensity to develop hypothyroidism during the same. No treatment is required by them for Tab+ status. Negro et al[18] demonstrated a significant decrease in the number of patients with postpartum thyroid depression when treated with selenium 200 μg/day, but the increased risk of developing type 2 diabetes mellitus in this group[19] made this recommendation unacceptable.

Several studies conducted in USA reported a 2 to 3% incidence of hypothyroidism among healthy, nonpregnant females of child-bearing age group.[11,12] Around 0.3 to 0.5% of these are classified in the OH group, and the rest in the SCH category. These values are likely to higher in countries with iodine deficiency.

Pregnancy is a state with increased thyroid hormone requirements. As a result, around 50 to 85% of previously hypothyroid women (on treatment) need to increase their dose of L-thyroxine, postconception.[15-17] This adjustment should be made as soon as possible after the pregnancy is confirmed and usually an increment in dose by 25 to 30% is required. This can either be achieved by increasing the dosage as a whole or by taking 2 extra tablets of the previous treatment per week. They are followed up the same way as newly diagnosed OH or SCH cases during pregnancy. Following delivery, the dose of L-thyroxine should be decreased to the preconception dose and serum TSH levels checked around 6 weeks postpartum.

Although, untreated OH is associated with adverse maternal and fetal outcomes, there are no data to suggest that adequately treated patients have any increased morbidity or mortality from the same. Therefore, there is no indication for additional testing or surveillance in such patients.

Hyperthyroidism can also complicate pregnancies, although its incidence is lesser than hypothyroidism. Gestational hyperthyroidism is the commonest cause accounting for 1 to 3% cases and is characterized by 'transient hyperthyroidism, limited to the first half of pregnancy characterized by elevated fT4 or adjusted T4 and suppressed or undetectable serum TSH, in the absence of serum markers of thyroid autoimmunity.[22] It is thought to occur because of high hCG levels and may be associated with hyperemesis gravidarum, multiple gestation, hydatidiform mole or choriocarcinoma.[23,24] Grave's disease is the second most common cause, accounting for 0.1 to 1% cases[20,21] and can either be diagnosed for the first time during pregnancy or present as a recurrent episode. Other causes include toxic multinodular goitre, toxic adenoma and factitious thyrotoxicosis.

The differentiation between gestational hyperthyroidism and Grave's disease can be made on the basis of clinical signs of Grave's disease, like goiter and endocrine ophthalmopathy. If in doubt, the determination of TSH receptor antibody (TRAb) is indicated as it will be absent in the former and present in the latter. There is inconclusive evidence for the use of thyroid ultrasound for the same in pregnancy, whereas the use of radioactive iodine uptake/scanning is contraindicated.[5]

The management of gestational hyperthyroidism depends upon the severity of symptoms that it produces. Hyperemesis gravidarum should be treated with fluids to prevent dehydration and antiemetics. Antithyroid drugs (ATDs) are not warranted since the serum T4 levels return to normal in 14 to 18 weeks period of gestation and studies found that the obstetrical outcome was not improved in cases that were treated with antithyroid drugs for the same.[25]

Unlike gestational hyperthyroidism, those due to Grave's disease needs treatment with ATDs and the obstetrical and medical complications are directly related to the control of hyperthyroidism and the duration of euthyroidism during pregnancy.[26-29] Poor control is associated with an increased incidence of miscarriages, pre-eclampsia, prematurity, low birth weight, intrauterine growth restriction, still birth, thyroid storm and maternal congestive heart failure.[30] Propylthiouracial (PTU) is preferred for treatment in the 1st trimester and then switched to carbimazole/methimazole for the subsequent trimesters. This is because PTU has not been associated with teratogenic effects that have been associated with the use of carbimazole/methimazole, but it is associated with the risk of hepatotoxicity, which may occur any time during the treatment with PTU. Beta blockers, like propranolol are used for controlling the hypermetabolic symptoms, the dose titration according to the clinical symptoms. They can usually be safely withdrawn in 2 to 6 weeks as prolonged use has been associated with intrauterine growth restriction, fetal bradycardia and fetal hypoglycemia.[31]

All ATDs cross the placenta and, therefore, the aim is to maintain the fT4 values at or just above the upper limit normal values using the smallest possible dose, in order to avoid harmful effects on the fetus. The fT4 values should be monitored every 2 to 6 weeks. Thyroidectomies are rarely indicated (allergy/contraindication to ATDs, non-compliance, large dose required) and should be performed in the 2nd trimester, if needed.

In all hyperthyroid cases, a determination of serum TRAb around 24 to 28 weeks is advised as it is helpful in detecting the pregnancies at risk of fetal hyperthyroidism. A value above three times the upper limit of normal is an indication for the close follow-up of the fetus. Follow-up of the fetus with serial ultrasounds can be performed in such cases. However, cordocentesis should not be performed unless fetal goiter is detected in women on ATDs, to determine whether the fetus is hyper- or hypothyroid. This is because cordocentesis is associated with both fetal morbidity and mortality.[32,33]

Breastfeeding is safe in mothers taking ATDs in moderated doses. Methimizole can be given in doses up to 20 to 30 mg/day while PTU is safe upto doses of 300 mg/day. They should be administered following the feed in divided doses.

Iodine requirement is increased during pregnancy because of increased thyroid hormone production, increased renal iodine excretion and fetal iodine requirements.[34] Women who had adequate iodine intake before and during pregnancy have adequate iodine stores and, therefore, have no difficulty in adapting to the increased demands. However, individuals with inadequate stores gradually burn them out during pregnancy and may become deficient. This may lead to fetal and maternal goiter and with increased rates of miscarriage, stillbirth, perinatal and infant mortality. The cognitive function of the infant is affected[37,38] as normal levels of thyroid hormone are required for the neuronal migration and myelination of the fetal brain. Children born to severely iodine deficient mothers during pregnancy exhibited cretinism, characterized by profound mental retardation, motor rigidity and deaf mutism. It is the leading cause of preventable mental retardation worldwide. Lactation is also associated with increased demands.[35,36] Spot urinary iodine samples are generally used for the determination of iodine status in the general population with levels <150 μg/l considered as deficient.

Therefore, women with iodine deficiency should receive iodine supplementation as it decreases the chances of the aforementioned adverse outcomes. This should be instituted early because majority of the fetal development occurs in the 1st trimester. As per the WHO, the recommended total dietary intake of iodine is 250 μg/day.[39] At the same time, excessive consumption of iodine is also to be avoided for the fear of fetal hypothyroidism (Wolff-Chaikoff effect) and guidelines suggest against exceeding an intake of 500 to 1100 μg/day.[5]

Postpartum thyroiditis (PPT) is defined as the occurrence of thyroid dysfunction in previously euthyroid women prior to pregnancy, in the 1st postpartum year.[40] It is found in about 8.1% women and this prevalence varies from one region to another.[41] Classically, it is characterized by transient thyrotoxicosis followed by transient hypothyroidism, finally followed by return to euthyroid state by the end of the 1st postpartum year.[42] The initial thyrotoxic phase usually occurs 3 months after the delivery and is characterized by nervousness, irritability and palpitations. These symptoms, however, most of the times are not attended to and attributed falsely to anxiety neurosis occurring especially after the birth of a female child. This phase is controlled with beta blockers like propranolol and does not require antithyroid treatment. Hypothyroid phase follows this and lasts for approximately 2 to 6 months. It is characterized by impaired concentration, poor memory and decreased energy and these again are falsely attributed to depression on account of maladjustment in the family after the arrival of the baby. This phase should be treated with thyroxine, which can usually be withdrawn in a year. Ten to twenty percent patients with postpartum thyroiditis become permanently hypothyroid. Therefore, yearly screening with serum TSH is recommended in women with a prior history of PPT.

PPT is considered as an exacerbation of an underlying auto immune thyroiditis, aggravated by the immunological rebound that follows the partial immunosuppression of pregnancy.[43,44] It is associated with the presence of anti-thyroid antibodies in the 1st trimester, with increased titres conferring an increased likelihood of the same.[45] Women suffering from other auto immune disorders like type 1 diabetes mellitus[46,47] and systemic lupus erythematosus[48] also have an increased risk. There is a 70% recurrence rate of PPT in subsequent pregnancies among individuals who recover from it.[49]

Spontaneous pregnancy losses and miscarriages are known to occur in around 17 to 31% pregnancies[50] and are a significant burden to the parents both emotionally and because of its propensity to cause bleeding, infections and pain. Poorly controlled diabetes mellitus and thyroid dysfunction can result in increased risk of pregnancy losses. Some studies have shown an association between the presence of thyroid antibodies (TPO and Tg) and an increased risk of pregnancy loss,[51,52] even among euthyroid women, while some did not agree with this relation.[53] A meta-analysis was conducted which found a clear association between thyroid antibodies and spontaneous abortion but did not prove causality. Therefore, there is insufficient evidence to decide whether or not to screen all pregnant women for the presence of thyroid antibodies in the 1st trimester. This holds true even for women with a history of recurrent abortions and to the question whether or not to treat such women with L-thyroxine.

Thyroid nodules and thyroid cancer can present in pregnancy posing many added challenges both to the clinician and the mother. Their prevalence was found to be roughly between 3 and 21%[52,54,55] and was found to increase with increasing parity. They were found to usually increase in size as the pregnancy progressed, returning to their pre-pregnant state postpartum[54,56] while sometimes a new nodule may develop during the course of the pregnancy. Any patient discovered to have a thyroid nodule should be asked about any positive family history for the occurrence of a benign/malignant thyroid disease. A history of any irradiation to the head and neck region during childhood should also be sought. A thorough history about the occurrence of the nodule, its rate of growth should also be sought and

noted down. Ultrasound of the thyroid nodule is the investigation of choice as it helps in determining its features, thereby distinguishing benign from malignant, and also evaluates the cervical lymph nodes. Thyroid function tests should also be carried out in such patients, but they are usually normal. In addition, all nodules showing progressive increase in size should be investigated by an FNAC (safe in all trimesters of pregnancy). Radio-iodine uptake studies are contraindicated in pregnancy[57-59] and should never be carried out. Surgery in such patients should be deferred until postpartum in all patients with benign disease or well differentiated malignant ones unless the nodules show rapid growth, severe compressive symptoms develop or a large primary tumor or extensive lymph node metastasis is present.[5] This is because several studies conducted to find any adverse impacts of pregnancy on the prognosis of benign and well differentiated thyroid cancer did not any association.[60-66] However, if surgery is deferred, these women should undergo follow-up ultrasounds every trimester to assess for the tumor growth and any need for intervention. If required, surgery should be performed during the second trimester as it is safe and not associated with any increased fetal or maternal risk.[5]

To conclude, pregnancy acts, like a stress test for the thyroid gland and results in hypothyroidism is women who are iodine deficient or have limited thyroid reserve, and postpartum thyroiditis in previously euthyroid women with underlying Hashimoto's thyroiditis. However, still there is inconclusive evidence to recommend for or against the universal serum TSH screening at the 1st trimester visit of a pregnant woman.

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