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Good clinical practice advice: Thyroid and pregnancy☆

FIGO Working Group on Good Clinical Practice in Maternal–Fetal Medicine*,[a]

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PREMISE

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

Human chorionic gonadotropin (hCG), secreted by the placenta, also impacts thyroid function because it simulates thyroid-stimulating hormone (TSH) activity in vivo, thereby suppressing its secretion.[1,2] Evidence suggests that throughout pregnancy, TSH values are lower than in the pre-pregnant state, and may even be below the classical lower limit of 0.4 mIU/L.[3,4] hCG concentrations are increased to a greater extent in multiple pregnancies; therefore, the downward shift is even more significant in these cases. Since the levels of hCG decrease as the pregnancy increases, the levels of TSH follow the reverse trend. Therefore, trimester-specific cut-off values of TSH should be used for diagnosis of hyper- or hypothyroidism during pregnancy, rather than the usual values for non-pregnant individuals. The recommended reference ranges are 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester.[5]

Studies also report a significant decrease in the levels of free T4 with the progression of pregnancy.[3,6,7] Measurements of free T4 are complicated by the increased levels of thyroxine-binding globulin and decreased levels of albumin during pregnancy, which make the immunoassays unreliable.[8,9] The best method to assess free T4 during pregnancy is to measure T4 in the dialysate/ultrafiltrate of the serum samples employing on-line extraction/liquid chromatography or tandem mass spectrometry.[5] However, if these methods are unavailable, the clinician can employ any available technique, with the knowledge of its shortcomings. Notably, serum TSH is a superior indicator of thyroid function in pregnancy.[5]

HYPOTHYROIDISM

Primary maternal hypothyroidism is defined as the increase in serum TSH levels during pregnancy. Depending on the free T4 levels, it is further classified as overt hypothyroidism (OH; free T4 levels decreased) or subclinical hypothyroidism (SCH; normal fT4 levels). This distinction is important, as studies show a more consistent relationship between adverse maternal and fetal outcomes and OH and SCH. OH is associated with an increased risk of premature birth, low birth weight, and miscarriage. Some studies have shown a 22% increase in the risk of gestational hypertension,[10] whereas others have found detrimental effects on neurocognitive development of the fetus[11,12] SCH can also be associated with similar adverse effects, but the data are inconclusive.[10–14] Thus, all patients found to have overt hypothyroidism should be treated with oral L-thyroxine (other preparations are not recommended). The decision whether to treat subclinical hypothyroidism remains debatable. Both OH and SCH patients should be followed up with serum TSH levels every 4 weeks up to 16–20 weeks of gestation and then at least once between 26 and 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.[15] 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 in this group[16] made this recommendation unacceptable.

Several US studies reported a 2%–3% incidence of hypothyroidism amongst healthy, non-pregnant women of child-bearing age.[11,12] Around 0.3%–0.5% of these women 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, roughly 50%–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 an increment in dose of 25%–30% is usually required. This increment can achieved either by increasing the dosage as a whole or by taking two extra tablets of the previous treatment per week. Follow up should be done in the same way as for newly diagnosed OH or SCH cases during pregnancy. After delivery, the dose of L-thyroxine should be decreased to the preconception dose and serum TSH levels checked around 6 weeks postpartum.

Although if untreated overt hypothyroidism is associated with adverse maternal and fetal outcomes, no data suggest that adequately treated patients have increased morbidity or mortality. Therefore, there is no indication for additional testing or surveillance in such patients.

HYPERTHYROIDISM

Hyperthyroidism can likewise complicate pregnancies, although its incidence is lesser than hypothyroidism. Gestational hyperthyroidism is the most common cause, accounting for 1%–3% cases of hyperthyroidism, 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".[18–20] It is thought to occur because of high hCG levels and may be associated with hyperemesis gravidarum, multiple gestation, hydatidiform mole, or choriocarcinoma.[21,22] Grave's disease is the second most common cause of hyperthyroidism, accounting for 0.1%–1% cases,[23] and might be diagnosed for the first time during pregnancy or be 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, such as goiter and endocrine ophthalmopathy. If in doubt, the determination of TSH receptor antibody is indicated as it will be absent in gestational hyperthyroidism and present in Grave's disease. There is inconclusive evidence for the use of thyroid ultrasound for differentiation between gestational hyperthyroidism and Grave's disease in pregnancy, whereas the use of radioactive iodine uptake/scanning is contraindicated.[5]

Management of gestational hyperthyroidism depends upon the severity of symptoms produced. Hyperemesis gravidarum should be treated with fluids to prevent dehydration and antiemetics. Antithyroid drugs are not warranted since the serum T4 levels return to normal by 14–18 weeks of gestation, and studies found that the obstetric outcome was not improved in women treated with antithyroid drugs for gestational hyperthyroidism.[24]

Unlike gestational hyperthyroidism, that due to Grave's disease requires treatment with antithyroid drugs and the obstetric and medical complications are directly related to the control of hyperthyroidism and the duration of euthyroidism during pregnancy.[25–28] Poor control is associated with an increased incidence of miscarriages, preeclampsia, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure.[29]

Propylthiouracial is the preferred treatment in the first trimester, with a switch to carbimazole/methimazole for subsequent trimesters. This approach is because propylthiouracial has not been associated with the teratogenic effects that have been associated with carbimazole/methimazole, but it is associated with risk of hepatotoxicity, which may occur at any time during treatment. Beta blockers, such as propranolol, are used to control the hypermetabolic symptoms, with dose titration according to the clinical symptoms. These drugs can usually be safely withdrawn within 2–6 weeks since prolonged use has been associated with intrauterine growth restriction, fetal bradycardia, and fetal hypoglycemia.[30]

All antithyroid drugs cross the placenta and therefore the aim is to maintain the free T4 values at or just above the upper limit of normal using the smallest possible dose so as to avoid harmful effects on the fetus. The free T4 values should be monitored every 2–6 weeks. Thyroidectomies are rarely indicated (allergy/contraindication to antithyroid drugs, non-compliance, large dose required) and should be performed in the second trimester, if needed.

In all cases of hyperthyroidism, determination of serum TSH receptor antibody around 24–28 weeks is advised to facilitate detection of 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 with serial ultrasounds can be performed in such cases. However, cordocentesis should only be done if fetal goiter is detected in women receiving antithyroid drugs, to determine whether the fetus is hyper- or hypothyroid. This is because cordocentesis is associated with both fetal morbidity and mortality.[31,32]

Breastfeeding is safe in mothers taking antithyroid in moderated doses. Methimizole can be given in doses up to 20–30 mg/day, whereas propylthiouracial is safe up to doses of 300 mg/day. Both should be administered following the feed in divided doses.

REQUIREMENT OF IODINE

Iodine requirement is increased during pregnancy because of increased thyroid hormone production, increased renal iodine excretion, and fetal iodine requirements.[33] 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.[34] However, inadequate stores are gradually depleted during pregnancy, leading to deficiency. This deficiency may lead to fetal and maternal goiter and increased rates of miscarriage, stillbirth, and perinatal and infant mortality. The cognitive function of the infant is affected[35,36] as normal levels of thyroid hormone are required for the neuronal migration and myelination of the fetal brain. Children born to mothers with severe iron deficiency during pregnancy exhibited cretinism, characterized by profound mental retardation, motor rigidity, and deaf mutism. It is the leading cause of preventable intellectual disability worldwide. Lactation is also associated with increased demands.[37,38] Spot urinary iodine samples are generally used for the determination of iodine status in the general population, with levels less than 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. Supplementation should be instituted early because much fetal development occurs in the first trimester. As per WHO guidelines, the recommended total dietary intake of iodine is 250 μg/day.[36] At the same time, excessive consumption of iodine should also be avoided due to the potential of fetal hypothyroidism (Wolff–Chaikoff effect) and guidelines advise against exceeding an intake of 500–1100 μg/day.[5]

POSTPARTUM

Postpartum thyroiditis is the occurrence, in the first postpartum year, of thyroid dysfunction in previously euthyroid women.[39] It is found in about 8.1% women and this prevalence varies from one region to another.[40] Classically, postpartum thyroiditis is characterized by transient thyrotoxicosis followed by transient hypothyroidism, with an eventual return to a euthyroid state by the end of the first postpartum year.[41] The initial thyrotoxic phase usually occurs 3 months after delivery and is characterized by nervousness, irritability, and palpitations. However, these symptoms are mostly 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, such as propranolol, and does not require antithyroid treatment. A hypothyroid phase follows this and lasts for approximately 2–6 months. This hypothyroidism is characterized by impaired concentration, poor memory, and decreased energy, symptoms that are again falsely attributed to depression on account of maladjustment after arrival of the baby. This phase should be treated with thyroxine, which can usually be withdrawn in 1 year. 10%–20% patients with postpartum thyroiditis become permanently hypothyroid. Therefore, yearly screening with serum TSH is recommended in women with a prior history of postpartum thyroiditis.

Postpartum thyroiditis is considered an exacerbation of an underlying autoimmune thyroiditis, aggravated by the immunological rebound that follows the partial immunosuppression of pregnancy.[42,43] It is associated with the presence of antithyroid antibodies in the first trimester, with increased titers conferring an increased likelihood.[44] Women with other autoimmune disorders, such as type 1 diabetes[45,46] and systemic lupus erythematosus,[47] also have an increased risk. There is a 70% recurrence rate of postpartum thyroiditis in subsequent pregnancies amongst individuals who recover.[48]

Spontaneous pregnancy losses and miscarriages occur in around 17%–31% pregnancies[49] and are a significant burden to the parents, both emotionally and because of its propensity to cause bleeding, infections, and pain. Poorly controlled diabetes and thyroid dysfunction can result in increased risk of pregnancy losses. Some studies have shown an association between the presence of thyroid antibodies (antithyroid peroxidase and antithyroglobulin) and an increased risk of pregnancy loss[50–52] even amongst euthyroid women; however, others did not identify this relation.[53] A meta-analysis found a clear association between thyroid antibodies and spontaneous abortion, but did not prove causality. Therefore, there is insufficient evidence to determine whether or not to screen all pregnant women for the presence of thyroid antibodies in the first 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.

OTHER THYROID PROBLEMS IN PREGNANCY

Thyroid nodules and thyroid cancer can present in pregnancy, posing many added challenges to both the clinician and the mother. Prevalence of nodules and cancer was roughly between 3% and 21%[51,53] and increased with increasing parity. Both disorders mostly increased in size as the pregnancy progressed, returning to their pre-pregnant state postpartum[53]; sometimes a new nodule may develop during the course of the pregnancy.[54]

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 and its rate of growth should also be sought and recorded. 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 results are usually normal. In addition, all nodules showing a progressive increase in size should be investigated by fine needle aspiration cytology (safe in all trimesters of pregnancy).

Radioiodine uptake studies are contraindicated in pregnancy[55,56] and should never be performed. Surgery in such patients should be deferred until postpartum in all patients with benign disease or well differentiated malignant disease unless the nodules show rapid growth, severe compressive symptoms develop, or a large primary tumor or extensive lymph node metastasis is present.[5,57,58] This is because several studies investigating the adverse effects of pregnancy on the prognosis of benign and well differentiated thyroid cancer did not find an association.[57–62] However, if surgery is deferred, these women should undergo follow-up ultrasounds every trimester to assess for tumor growth and 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]

CONCLUSIONS

Pregnancy acts as 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 first trimester visit of a pregnant woman.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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