

REVIEW ARTICLE

Thyroid disorders during pregnancy and anesthetic considerations

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ABSTRACT

Our knowledge about thyroid function during pregnancy has made rapid strides in the recent past. However, there are not much published reports in anesthesia literature regarding these newer developments. Even though an anesthesiologist is not the primary care physician, he/she may occasionally encounter pregnant patients with thyroid dysfunction in routine practice of anesthesia. This article aims to update anesthesiologists about recent developments in understanding of thyroid physiology during pregnancy, effects of thyroid dysfunction on mother and fetus, interpretation of thyroid function tests as well as treatment and anesthetic considerations.

Key words: Thyroid disorders; Pregnancy; Anesthesia

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INTRODUCTION

The thyroid disorders are the second most common endocrine abnormality during pregnancy and it is well known that thyroid dysfunction during pregnancy can have deleterious effects on both mother and fetus. Last two decades have seen remarkable developments in this field which overlaps both obstetrics and endocrinology.¹ There are limited published data in the anesthesia literature regarding these new developments in the understanding of thyroid physiology during pregnancy, interpretation of thyroid function testing, treatment and its efficacy, monitoring of mother and fetus and anesthetic implications.

Even though anesthesiologist is not the primary physician for such patients, he/she may have to encounter these patients coming for obstetric and non-obstetric surgery during the course of pregnancy or labour analgesia or intensive care management. This review aims to summarise the recent developments, existing guidelines for management of thyroid dysfunction during pregnancy and their implications for the anesthesiologist in day to day anesthesia practice.

THYROID PHYSIOLOGY IN PREGNANCY

It is the hypothalamic-pituitary-thyroid (HPT) axis, which governs the thyroid physiology. The hypothalamus, via

thyroid releasing hormone (TRH), stimulates the pituitary which in turn produces thyroid stimulating hormone (TSH). The levels of TSH are controlled by negative feedback on hypothalamic pituitary axis by thyroxine (T_4) and triiodothyronine (T_3). TSH stimulates thyroid gland to produce T_4 and T_3 .^{2,3}

The physiological changes in the HPT axis during pregnancy include;

1. Human chorionic gonadotropin (HCG) being similar to TSH in having identical α subunits, stimulates release of T_4 and T_3 and causes transient decrease in TSH via negative pituitary feedback.¹
2. Increased levels of estrogen results in two to three fold increase in thyroid binding globulin (TBG), which lowers free thyroid hormone and stimulates HPT axis. Increased levels of TBG lead to increase in total T_4 levels starting at 8 weeks of gestation, which reaches a steady state by 16 weeks.¹
3. In second and third trimester, placental deiodinases converts T_4 to reverse T_3 thus enhancing the peripheral metabolism of thyroid hormone. A small amount of maternal T_4 and T_3 is also transferred to fetus via placenta for growth of fetus.
4. Increased urinary iodine excretion due to increased GFR, as well as increased thyroid hormone production increases iodine requirement during pregnancy.

HYPOTHYROIDISM AND PREGNANCY

Hypothyroidism is due to decreased production of thyroid hormones. It is the second most common endocrine disorder found in pregnancy. The incidence is 0.3%.⁴ Globally, iodine deficiency is the leading cause but in developed countries Hashimoto thyroiditis ranks first.⁵ The vague symptoms of hypothyroidism are similar to pregnancy concerns including fatigue, cold intolerance, constipation, muscle cramps, insomnia, weight gain, carpal tunnel syndrome, hair loss, voice changes and slower thinking.⁶ Other findings may include dry skin, peri-orbital edema and decreased deep tendon reflexes. There can be physiological enlargement of thyroid due to increased vascularity and glandular hyperplasia. The increase in size is 10-15% and is not typically apparent on physical examination.^{7,8,9}

Subclinical hypothyroidism

The prevalence of subclinical hypothyroidism in our population is about 14.3%. These patients manifest clinically with vague and nonspecific symptoms. It has been associated with hypercholesterolemia, atherosclerosis, cardiovascular mortality, infertility, poor obstetric outcome, neuropsychiatric symptoms, unprovoked deep vein thrombosis and common bile duct stones.^{10,11,12}

Isolated maternal hypothyroxinemia

Patients with isolated maternal hypothyroxinemia have a normal TSH level but their free T_4 is less than 0.86 ng/dl. In the first half of pregnancy, the prevalence is 1.3%. As perinatal outcome is not much affected, treatment of these patients is not warranted.¹⁵

Interaction with pregnancy

Hypothyroid women show decreased fertility rate due to neuroendocrine and ovarian dysfunction and women who conceive exhibit symptoms at a lower level of TSH. Immunosuppression seen in pregnancy may improve Hashimoto thyroiditis, albeit temporarily.⁸ There can be a greater risk of early and late obstetric complication such as miscarriage, anaemia, gestational hypertension, placental abruption, premature delivery and postpartum haemorrhage.^{13,14} Ghahia eshoor et al., demonstrated an association between increase in TSH to five times the normal at 11 to 13 weeks of gestation and subsequent development of late-PE. This association was independent of autoimmune mechanisms.¹⁵

As the presence of an autoimmune disease increases the development of other autoimmune diseases, there is a 5% to 8% prevalence of hypothyroidism in type I diabetes mellitus; women who have type I diabetes are at a 25% higher risk of developing postpartum thyroid dysfunction.⁵

Thyroid function tests in pregnancy

The physiological changes in pregnancy makes interpretation of laboratory tests difficult. The increase in TBG results in increase in total T_3 (TT_3) and total T_4 (TT_4). Free T_3 (FT_3) and free T_4 (FT_4), which reflect the thyroid function in pregnancy may also be altered by TBG.

The free T_4 index (FT_4I) is an indirect measure of FT_4 and accounts for increase in TBG.

$$FT_4I = TT_4 \times RT_3U$$

The reported reference value for FT_4I is 4.5-12.5mcg/dl.

The laboratory values associated with hypothyroidism are increase in TSH, low FT_4 , FT_4I and variable presence of thyroperoxidase antibodies (TPO). TSH and FT_4/FT_3 are used to assess and follow thyroid diseases in pregnancy.⁸ The reference range of TSH varies more in pregnancy as compared to general population. As evidenced in several studies it varies in accordance with gestational age, number of foetuses, laboratory and testing methods.¹⁴

Upper limit of TSH should be 2.5 mIU/L in 1st trimester and 3mIU/L in 2nd and 3rd trimesters. The lower limit could be 0.1 mIU/L in 1st trimester and 0.2 mIU/L in 2nd and 3rd trimesters. Failure to apply these specific reference ranges may result in underestimation of hypothyroidism and overestimation of hyperthyroidism. The debate regarding the pros and cons of universal screening is ongoing and case finding approach is still recommended although, few studies have shown that chances of missing pregnant hypothyroid women amounts to one –third if testing is done only for high risk groups.^{4,16} Pregnant women with history of thyroid disease, family history of thyroid disease, known autoimmune disease, presence of goitre, previous history of neck radiation and history of medications which cause thyroid disturbances should be screened. If the serum TSH is ≥ 3 mIU/L, tests have to be repeated in different labs along with FT_4 and TPO. Levothyroxine should be given awaiting the lab reports. If reports suggest euthyroid state, then levothyroxine should be stopped and patient is considered euthyroid. If TSH is > 3 mIU/L and FT_4 is normal, then patient should be tested periodically throughout the pregnancy. If TSH > 3 mIU/L along with low FT_4 , then levothyroxine is continued and the dose is titrated to maintain TSH level in the range of 0.5-2.5 mIU/L. TSH level should be checked every 6 to 8 weeks in pregnancy.^{8,17,18}

Medical management

In women with pre-existing hypothyroidism, there is 30-50% increase in requirement of levothyroxine during the first trimester. This is due to increased T_4 metabolism, elevated TBG as well as inhibition of thyroid hormone (TH) absorption from the gut by prenatal iron supplements.

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This can be minimized by administering iron supplements and TH four hours apart. In women diagnosed with hypothyroidism during pregnancy, levothyroxine should be started at a dose of 1-2 mcg/kg/day. TSH levels should be reassessed 4-6 weeks following the dose change with treatment goal of TSH in the range of 0.5-2.5 mIU/L. In case of overt hypothyroidism diagnosed in pregnancy, T_4 should be normalised as rapidly as possible by using two to three times the estimated final daily dose. It is important to monitor and treat the patient according to biochemical values of the hormones rather than by clinical judgement.^{2,8,13,14}

Anesthetic management

Clinical manifestations of hypothyroidism affecting anesthetic management are reversible myocardial dysfunction, reversible defects in hypoxic and hypercarbic ventilatory drives, obstructive sleep apnoea, paraesthesia, increased cerebrospinal fluid protein concentration, hyponatremia, anaemia, abnormal coagulation profile, increased peripheral nociceptive thresholds and coronary artery disease.^{19, 20}

During pre operative preparation, anxiolytics and sedatives should be avoided. However, administration of antihistamines like ranitidine and oral sodium citrate solution along with metoclopramide are considered safe. Severe hypothyroidism should be managed with IV T_3/T_4 but, if they are not available, oral T_3 is the mode of choice.²¹ Hypothermia should be prevented in the operation room as well as in the post operative period.

Decreased intravascular volume, preload, cardiac output and blunted baroreceptor response make the patient sensitive to cardio depressant effects of anesthetics.²² During surgical stress, hydrocortisone should be given.^{19, 23}

Regional anesthesia should be favoured over general anesthesia. Nerve stimulators may not be useful clinically due to abnormal response to the peripheral nerve stimulator. Although hypothyroidism is associated with qualitative platelet dysfunction, epidural hematoma is a theoretical risk and presence of normal coagulation should be confirmed before regional anesthesia.⁸ Vasopressor response is normal for epinephrine but, decreased for phenylephrine.

Myxedema coma in pregnancy

Myxedema coma, is a life threatening form of decompensated hypothyroidism. Most commonly it is seen in older women but few case reports have confirmed its occurrence in pregnancy. The extremely high mortality rate (25-60%) makes it necessary for early recognition and treatment. Although encountered rarely, a healthy degree of suspicion of the 'worst first' mentality must be maintained to prevent poor outcomes in these patients.

Precipitating factors are hypothermia, infections and septicaemia, cerebrovascular accidents, congestive heart failure, gastrointestinal bleeding, trauma and fractures, drugs (anesthetics, sedatives, tranquilizers, narcotics, amiodarone, and lithium) and withdrawal of thyroid supplements.²⁴

Clinically patient may present with mental status changes including lethargy, cognitive dysfunction, and even psychosis. Hypothermia in spite of infection is the hallmark feature of myxedema coma. Hyponatremia, hypoventilation, and bradycardia can also occur. A high mortality rate, even with appropriate treatment, mandates management in the intensive care unit where proper ventilatory, electrolyte, and hemodynamic support can be given. Passive rewarming, broad spectrum antibiotic coverage and corticosteroids may also be needed. The definitive treatment is thyroid hormone replacement administered as IV T_4 , 200 to 500 mcg as an initial bolus followed by 50-100 mcg daily. Few centers suggest addition of IV T_3 , 10-25 mcg every 8 hours if available. Rapid thyroid hormone replacement may precipitate myocardial infarction, hence caution should be exercised in those with underlying ischemic heart disease. Treatment of the precipitating cause like an infection is critical for rapid recovery.^{25, 26}

HYPERTHYROIDISM

Hyperthyroidism occurs in 0.2% of pregnant women. Hyperthyroidism is defined as excessive thyroid hormone production by the thyroid gland.

Normal pregnancy is also associated with certain changes in the HPT axis which favours increased thyroid hormone production, though this does not produce clinical symptoms and signs of thyrotoxicosis. HCG has some structural homology with TSH and stimulates TSH receptors in the thyroid tissue, thus increasing T_4 levels and suppressing TSH by negative feedback from T_4 .²⁷ Increased estrogen leads to higher level of TBG thus increasing total T_4 levels to 150% above the normal non-pregnant reference levels.⁸

The causes of hyperthyroidism in pregnancy can be divided into immune and non-immune categories.¹ The most common cause of non-immune hyperthyroidism is Gestational thyrotoxicosis. It is due to high levels of HCG causing increase in serum FT_4 and suppressed or undetectable TSH; usually associated with hyperemesis gravidarum.²⁸ It can also be caused by molar pregnancy associated with very high levels of HCG.

The commonest cause of hyperthyroidism during pregnancy is Graves' disease,²⁹ an autoimmune hyperthyroidism disorder due to stimulation of thyroid gland by the thyroid stimulating hormone receptor antibody (TSHRab). Other causes can be toxic solitary thyroid nodule, multinodular goiter, exogenous thyroid hormone, drugs like amiodarone

and subacute thyroiditis. The clinical course of Grave's disease varies throughout the pregnancy, with exacerbation during first trimester and post partum period and remission during second and third trimester due to general immunosuppression of pregnancy.³⁰

Both pregnancy and hyperthyroidism are associated with increased metabolic rate. This causes difficulty in recognition of Graves' disease. Some of the symptoms of this disease are similar to those presenting in normal pregnancy like heat intolerance, shortness of breath, weakness, nervousness, emotional lability and increased pulse rate. This makes it difficult to diagnose hyperthyroidism in pregnancy. Careful clinical examination may reveal presence of goiter, ophthalmopathy, pretibial myxoedema and clubbing which are exclusive to Graves' disease.⁸ Thyroid function testing is beneficial, but one must keep in mind the effect of gestational age on TSH and T_4 , as discussed earlier. It is important not to misdiagnose hyperthyroidism as TSH levels are normally suppressed in pregnancy. According to current evidence, subclinical hyperthyroidism (suppressed TSH with normal T_4) does not adversely affect pregnancy, hence treatment is not advised.²⁹

Interaction with pregnancy

Clinically and biochemically diagnosed hyperthyroidism during pregnancy needs to be treated as it can have adverse effects on both mother and fetus. Commonest clinical sequelae in mother are hypertension and preeclampsia; they can also develop pulmonary edema and congestive cardiac failure in late pregnancy.²⁷ Uncontrolled hyperthyroidism can lead to preterm labor and delivery, placental abruption and can rarely lead to thyroid storm. Adverse effects on fetus include fetal tachycardia, small for gestational age babies, accelerated bone maturation, prematurity, still births and possibly congenital malformations. In Graves' disease, thyroid stimulating antibodies readily cross placenta and stimulate fetal thyroid with the resultant fetal or neonatal hyperthyroidism. Fortunately, this occurs only with very high levels of thyroid antibodies.

Medical Management

Maintenance of euthyroid state in the mother cannot be overemphasized. The mainstay of treatment of hyperthyroidism in pregnant patient remains antithyroid drugs.^{4,31,32} Radioactive iodine treatment is contraindicated in pregnant women because of irreversible damage to the fetal thyroid gland.³³ Surgery- subtotal thyroidectomy- can be considered as if patient is allergic to or not responding adequately to antithyroid drugs, patient is noncompliant to medications, or a large goiter is causing symptoms of dysphagia or airway obstruction. It is done rarely during pregnancy due to risks of both surgery and anesthesia to the mother and fetus. The optimal timing for surgery is the

second trimester. A case report recounts an incidence of thyroidectomy because of acute respiratory failure due to enlarged thyroid during 20th week of gestation, followed by uneventful pregnancy.³⁴ There are also case reports of cesarean section combined with thyroidectomy in patients with severe symptoms.³⁵

Antithyroid medications cross the placenta in small amounts and can decrease the fetal thyroid hormone production, so the lowest possible dose to achieve adequate metabolic control is preferred.^{27,36}

Propylthiouracil (PTU) is the preferred drug during pregnancy, because methimazole is associated with rare teratogenicity resulting in aplasia cutis and choanal or esophageal atresia. However, recently there have been reports of severe hepatotoxicity with the use of PTU. Therefore, it is suggested to start treatment with PTU during the first trimester and switch over to methimazole at the beginning of second trimester. The treatment should begin with the lowest possible doses of antithyroid drugs, so that free T_3 and T_4 are in the high normal range.³⁷ Maintaining the hormone levels in this range will minimize the risk of fetal hypothyroidism and goiter. Thyroid function tests should be assessed monthly and antithyroid drug dose should be adjusted as required.

The initial recommended dose of PTU is 100-450 mg per day, divided into three daily doses, depending on patient's symptoms and thyroid function test results. Methimazole is prescribed at 10-20 mg per day in once daily dose. The most common side effects of anti-thyroid drugs are mild hypersensitivity skin reactions, transient leukopenia and rarely, agranulocytosis and acute cholestatic hepatitis.

Beta blocking agents, such as propranolol, 10 – 40 mg every four to six hours or 25- 50 mg daily, can be given to treat hyperadrenergic symptoms. Short term use is recommended as there are reports of impaired fetal growth with long term use of beta blockers.

Even though there are advanced techniques for monitoring of fetal thyroid gland, monitoring of maternal thyroid status is a more clinically practical index of fetal thyroid status. Serial fetal ultrasound examinations should be done. They can reveal fetal goiter, fetal tachycardia (>170 bpm for 10 minutes), intrauterine growth retardation, features of congestive cardiac failure, accelerated skeletal maturation and fetal hydrops.³⁸

Anesthetic considerations

It is a well known fact that any hyperthyroid patient should be rendered euthyroid before elective surgery. But anesthesiologists can encounter inadequately treated patients during emergency situation, for example emergency caesarean section. Such patients have hypermetabolic and hyperdynamic states which need to be optimized

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as far as possible with intravenous beta blockers and antithyroid drugs. Even intravenous magnesium has been used for its vasodilatory effect without depression of the myocardium.³⁹

Problems one need to keep in mind are: 1) hyperdynamic circulation leading to high output cardiac failure 2) cardiac dysrhythmias 3) difficult airway associated with huge goiter and 4) thyroid storm.

In a pregnant patient presenting with goiter, airway can be difficult because of accompanying pregnancy induced changes like generalised weight gain, increase in breast size, respiratory mucosal edema and increased risk of pulmonary aspiration. Awake fiberoptic intubation can be preferred choice of intubation in such patients.³⁵ Hemodynamic responses to laryngoscopy and intubation can be exaggerated and detrimental. Inadequate depth during general anesthesia can lead to hypertensive crisis and dysrhythmias which can cause considerable morbidity.

Regional anesthesia can be preferred for caesarean section or other lower abdominal procedures; it is easier and safer in such patients. It also avoids manipulation of a potential difficult airway and cardiovascular problems due to inadequate depth.

Thyroid storm and Heart failure

Pregnancy can be a potential precipitant of rare complications like thyroid storm or heart failure.⁴⁰ Thyroid storm is an acute, severe, life threatening hypermetabolic state and is rare in pregnancy. Pulmonary hypertension and cardiac failure due to thyroxine-induced cardiomyopathy are relatively more common. Pregnant women with uncontrolled hyperthyroidism have minimal cardiac reserve and high output cardiac failure can be precipitated by preeclampsia, anemia, sepsis or a combination of these factors.

Treatment of both conditions should be carried out in an intensive care unit. In thyroid storm- along with supportive

treatment- anti-thyroid drugs (PTU initially 1000 mg orally or through nasogastric tube), iodine (5 drops of super saturated potassium iodide every 8 hours or lugol's solution 10 drops every 8 hours), steroids (dexamethasone 2mg intravenously every 6 hours for four doses) and beta blockers (propranolol/esmolol/labetalol 1mg/min intravenously repeated until tachycardia settles) should be given.^{41, 42} In addition to above measures, diuretics can be used in heart failure patients. Coexisting preeclampsia, anemia or sepsis should be managed aggressively and appropriately.

Post partum thyroiditis

Postpartum thyroiditis is an inflammation of thyroid gland resulting in transient thyrotoxicosis followed usually by hypothyroidism. It occurs in 4 to 10% of women during first year postpartum.¹⁸ It can often go undiagnosed as symptoms resemble those of postpartum blues, so one needs to be vigilant when diagnosing.

THYROID CANCER

Thyroid cancers are the most common endocrine malignancies,⁴³ accounting for 1% of all cancers. Three out of four tumors occur in women; half present during the reproductive years. Therefore, for any solitary or dominant nodule in the thyroid gland, FNAC is recommended and is safe during pregnancy. Serum TSH and free T₄ levels should be obtained and ultrasonography can be used to characterize the lesion. A benign lesion can be followed conservatively and re-aspirated if the cystic lesion enlarges again. If a lesion is frankly malignant or suspicious for papillary cancer, surgery should ensue at the earliest safe period. Patients should be maintained on thyroid replacement therapy with monitoring of TSH and FT₄ levels every 8 weeks.⁵

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