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Sri Lanka College of Obstetricians and Gynaecologists

Thyroid disease in pregnancy and the postpartum period

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Background

Thyroid disease in pregnancy, Hypothyroidism and Hyperthyroidism (thyrotoxicosis) can lead to adverse pregnancy outcomes. It can also affect foetal development and contribute to negative outcomes in infancy and childhood[1].

Worldwide, the most common cause of hypothyroidism is an inadequate dietary intake of iodine. Universal Salt Iodination (USI) was first introduced in Sri Lanka in 1995, which led to a remarkable decrease in the prevalence of iodine deficiency and goitre[2]. Updated data regarding the prevalence of thyroid disease in the Sri Lankan population is relatively sparse. According to population-based studies done in Sri Lanka, prevalence of goitre was found to be around 6.8% while that of subclinical hypothyroidism was found to be approximately 4-5% with females being the most commonly affected group[3,4,5]. It is also interesting to note that the prevalence of the presence of thyroid auto-antibodies has been observed to be rising following the introduction of USI[4].

Physiological changes of thyroid function during pregnancy

During an average pregnancy, the volume of the thyroid gland increases by 10-30% and the iodine uptake rises by three-fold. Maternal Thyroid-Binding Globulin level increases due to the increased hepatic synthesis under oestrogen stimulation. TSH receptors in the thyroid gland are weakly stimulated by Human Chorionic Gonadotropin (hCG) hormone. Therefore, the total thyroxine (T4) and triiodothyronine (T3) levels increase, although free T4 levels are altered slightly and usually fall during the late course of pregnancy[1].

During pregnancy, Thyroid Stimulating Hormone (TSH) levels initially rise with conception and then fall during the first trimester as the increased T4, T3 levels suppress the hypothalamic Thyroid Releasing Hormone (TRH) thus in turn suppressing the release of TSH from the pituitary gland[6].

After the first trimester, TSH levels normalize to baseline levels and can increase gradually in the third trimester due to the presence of Placental Deiodinase. In Hyperemesis Gravidarum, increased hCG levels can result in a benign transient biochemical hyperthyroidism in around 60% of cases.

Foetal thyroid gland starts functioning at about 12 weeks after gestation. However, maternal T4 is transferred to the foetus throughout the pregnancy and is considered to be important factor for foetal neural development. This is of particular significance during the first 12 weeks. At birth, about 30% of umbilical

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cord-measured T4 is derived from the maternal thyroid. Therefore, a history of anti-thyroid drugs or presence of Thyroid Receptor Antibodies in the mother should be communicated to the neonatal physician.

Thyroid function tests during pregnancy

SLCOG recommends the following cut-off limits in Thyroid Function Tests during pregnancy in accor-dance with the reference ranges accepted by the American Thyroid Association[7].

Hormone	1st trimester 2nd trimester	3rd trimester
TSH	0.1 - 2.5 mIU/L 0.2 - 3.0 mIU/L	0.3 - 3.0 mIU/L
Total T 4	6.5 - 10.1 ug/dl 7.5 - 10.3 ug/dl	6.3 - 9.7 ug/dl
Total T 3	97 - 149 ng/dl 117 - 169 ng/dl	123 - 162 ng/dl
Free T 4	0.8 - 1.7 ng/dl 0.6 - 1.0 ng/dl	0.5 - 0.8 ng/dl
Free T 3	4.1 - 4.4 pg/ml 4.0 - 4.4 pg/ml	4.0 - 4.4 pg/ml

Early Gestational Hyperthyroidism (EGH)

EGH is a recognized new entity in the spectrum of thyroid disease in pregnancy, usually presenting with Hyperemesis Gravidarum and mildly symptomatic hyperthyroidism. It is more common in people of Asian descent. Management includes supportive care and hydration. We recommend not starting antithyroid medications for this condition. However, many with symptoms would require beta blockers to control symptoms which can generally be discontinued in the second trimester[1].

With regard to thyroid functions, four clinical entities can be deduced apart from the normal euthyroid status. These are

- Overt Hyperthyroidism
- Subclinical Hyperthyroidism
- Overt Hypothyroidism
- Subclinical Hypothyroidism

Table 1 demonstrates the associated changes in thyroid function tests for each condition.

Table 1. Pregnancy associated changes in thyroid function tests in thyroid disorders indicated above

Maternal Status	Thyroid Stimulating Hormone (TSH) Status	Free T4 Level
• Overt Hyperthyroidism	Decrease	Increase
• Subclinical Hyperthyroidism	Decrease	Unchanged
• Overt Hypothyroidism	Increase	Decrease
• Subclinical Hypothyroidism	Increase	Unchanged

Table 1. Abbreviations: T4, thyroxine; TSH, thyroid-stimulating hormone. *The level of TSH decreases in early pregnancy because of weak TSH receptor stimulation due to substantial quantities of human chorionic gonadotropin during the first 12 weeks of gestation. After the first trimester, TSH levels return to baseline values.

Hyperthyroidism

Hyperthyroidism occurs in about 1 in 500 pregnancies and is most commonly due to Graves' Disease. De novo cases can be due to solitary toxic adenomas, toxic multinodular goitre, subacute thyroiditis, acute thyroiditis (viral/de Quervain's) or due to medications (Iodine/Lithium/Amiodarone). Increased thyroid activity in pregnancy can lead to the aggravation of Grave's thyrotoxicosis in the first trimester and puerperium. Generally, auto-immune thyroid diseases are relatively quiescent during pregnancy due to the relatively immune-suppressive state of pregnancy.

Well controlled disease can achieve good maternal and foetal outcomes. If untreated however, can lead to miscarriage, fetal loss, fetal growth restriction, preterm labour and increased perinatal mortality. Thyroid antibodies can cross the placenta and result in foetal and neonatal thyrotoxicosis.

Hyperthyroidism will lead to maternal sinus tachycardia, supraventricular tachycardia, atrial fibrillation, thyroid storm and heart failure.

Clinical features

Resembles early normal pregnancy symptoms; heat intolerance, palpitations, tachycardia, palmar erythema, vomiting, emotional lability and goitre. De novo cases usually present in the early second trimester.

Discriminating features;

- Weight loss
- Persistent tachycardia
- Sleeping pulse > 100 per minute
- Tremor
- Lid lag
- Exophthalmos
- Symptoms predating the pregnancy

Management

• Normal ranges for pregnancy trimesters should be used for assessment and the diagnosis is by raised levels of free T4 and T3 and suppressed TSH.

Antithyroid Drugs (ATD)

- Medications used are Carbimazole, Methimazole and Propylthiouracil (PTU).
- Aim to achieve rapid and optimal control with the lowest dose of medications to maintain euthyroid state with free T4 level at upper limit of normal range.
- Antithyroid medication response is delayed and takes 3-4 weeks. Once response is achieved, dose should be gradually reduced to maintenance dose for 12-18 months[6].

Eg: Carbimazole starting dose 15-40 mg, then reduced to 5-15mg,

PTU starting dose 150-400 mg, then reduced to 50-150 mg.

- Both drugs can cross the placenta (PTU less than Carbimazole) and can result in foetal hypothyroidism and goitre.
- Both drugs can cause congenital abnormalities (2-4%) although more severe with Carbimazole.
- Carbimazole and Methimazole, when used in the first trimester can cause a rare side effect; Aplasia Cutis of the foetus (Foetus is born with the absence of certain layers of skin, most often on the scalp, but also on the trunk, and/or arms and legs).
- PTU can cause a rare complication i.e. liver failure of the mother (1 in 10,000).
- Doses below 15mg/day of Carbimazole and 150mg/ day of PTU are unlikely to cause foetal effects.
- We recommend starting PTU for newly diagnosed cases in the first trimester and then converting to Carbimazole in the second trimester and onwards. It is preferable to continue low dose Carbimazole without changing drugs if already diagnosed and under control with Carbimazole since preconception period.
- "Block and replace" therapy is not recommended.
- Both drugs can cause a drug urticaria in 1-5% of patients and the medication should be changed to a different preparation.
- Rarely both drugs may cause agranulocytosis and result in neutropenia, thus patients should be monitored for symptoms with Full Blood Count at an early point of the treatment process.
- Grave's Disease can relapse in postpartum, therefore all mothers should be re-tested in 2-4 months after delivery.

- Breastfeeding is safe if it is on low doses of drugs and needs foetal thyroid function monitoring in the case of mother taking higher doses.

Beta Blockers

- Will provide symptom control in the early phase of treatment and during relapse. Eg: Propranolol 40mg three times daily.
- It will also reduce peripheral conversion of T4.
- Can be discontinued after the achievement of the antithyroid medication response. As it is used for a short duration, it will not cause harmful foetal effects.

Surgery

- Can be done for those who present with large goitre causing dysphagia and stridor, confirmed or suspected thyroid malignancy or if allergic to antithyroid medication. If indicated it is done in the second trimester. Need close follow up and treatment for hypothyroidism as 25-50% will be hypothyroid following surgery.
- 1-2% of patients will develop hypocalcemia due to removal of the parathyroid gland.

Radio-active Iodine

- As it is taken up by foetal thyroid and causes foetal thyroid ablation, radio-iodine therapy is contra-indicated in pregnancy and post-partum.
- Radio-iodine scans for diagnostic purposes are also contra-indicated in pregnancy and breastfeeding. Breastfeeding should be withheld for 24 hrs if radio iodine tests done postpartum.

Thyroid Storm – Diagnosis and Management

A rare disorder with a mortality rate of 8-25% which presents with multi-organ dysfunction. Symptoms include; pyrexia, tachycardia, arrhythmia, heart failure, delirium, stupor or coma, liver failure, vomiting and diarrhoea.

Precipitants; sudden withdrawal of ATD, following radio-iodine treatment, stress due trauma (surgery) or acute febrile illness. Thus, ensuring euthyroid status of the mother at the elective caesarean section or at labour is of paramount importance.

Diagnosis should be made clinically in severe-level thyrotoxicosis patients with evidence of decompensation. Burch-Wartofsky point scale or Japanese Thyroid Association categories can be used to decide on the need for aggressive treatment.

Supportive care, starting PTU recommended for control of thyroxin production from both in gland and peripheral conversion (preferred over Carbimazole/ Methimazole), beta blockers, glucocorticoid therapy with strict ICU / HDU care is useful for control of effect or symptoms and to revive decompensated systems.

Poor respondents should be offered plasmapheresis and emergency surgery[10].

Foetal/ Neonatal monitoring

- Transplacental passage of thyroid stimulating antibodies results in foetal or neonatal thyrotoxicosis which will cause a 25% mortality if untreated.
- Mothers known to be positive for thyroid antibodies, antibody level testing should be done in early pregnancy. If titers are high or do not fall with treatment, foetal ultrasound should be offered to detect foetal growth restriction in second and third trimesters. Looking for Goitre and tachycardia should be done after delivery. Thyroid function tests in cord blood and neonate should be performed[11].
- Foetal thyrotoxicosis should be treated with antithyroid medications to the mother, with thyroxine replacement if she is euthyroid.
- Neonate should be closely monitored by the Paediatric team. Following diagnosis of thyroid disease, it should be treated as soon as possible. However, the abnormalities will settle once maternal antibodies are completely cleared after around 4th month of life.

Subclinical Hyperthyroidism

Subclinical Hyperthyroidism is reported in about 0.8-1.7 percent of pregnant women[12,13]. Diagnosis is done using low TSH levels with normal free T4, T3 levels. This diagnosis not shown to be associated with an effect on pregnancy. Therefore, treatment is not recommended.

Hypothyroidism

Hypothyroidism affects around 1% of pregnancies. Most women will have a positive family history of auto-immune hypothyroidism and will be diagnosed and placed on treatment prenatally. Most common types are Atrophic Thyroiditis and Hashimoto's Thyroiditis (Auto-Immune Thyroiditis and goitre). Hashimoto's Thyroiditis is the most common cause of hypothyroidism in developed countries. In contrast, worldwide, the most common cause of hypothyroidism is the inadequate dietary intake of iodine.

Hypothyroidism can also be iatrogenic; due to radio-iodine therapy, thyroidectomy, and due to medications (Antithyroid drugs, Iodine, Lithium, Amiodarone). It can also be associated with other auto-immune diseases.

Hashimoto Thyroiditis is an autoimmune disease that destroys thyroid cells by cell and antibody-mediated immune responses. The pathology of the disease involves the formation of antithyroid antibodies that target and destroy the thyroid tissue, causing progressive fibrosis. Most patients develop antibodies to a variety of thyroid antigens, the most common of which is anti-thyroid peroxidase (anti-TPO, previously named Anti-microsomal antibody). Many also form antithyroglobulin (anti-Tg) and TSH receptor-blocking antibodies (TBII).

Pregnancy has no effect on hypothyroidism. Twenty-five percent of women will require higher requirements of thyroxine dosing during the course of the pregnancy. If untreated, it can lead to miscarriage, fetal loss, foetal anaemia and low birthweight. Foetal thyroid functions begin around the 12th week of gestation. Thus, the foetus is dependent on maternal thyroxine during early gestation. Therefore, if untreated, hypothyroidism and severe maternal iodine deficiency will affect fetal neuro-development leading to cretinism (condition of severe physical and mental retardation specifically due to deficiency of thyroid hormones during early pregnancy, hypothyroidism, spastic motor disorder and deaf mutism-congenital deafness that results in inability to speak). Untreated maternal hypothyroidism has a higher chance of low birthweight. In rare cases, maternal thyroid antibodies could cross the placenta and cause foetal hypothyroidism but this is extremely rare.

Mothers who are well controlled and euthyroid at conception can achieve good maternal and foetal outcomes.

Diagnosis of hypothyroidism is done when TSH level is over the reference range for the gestational age of pregnancy and the free T4/T3 levels are below the lower limit of normal.

Adverse perinatal outcomes could be reduced by appropriate therapy.

Clinical features

Symptoms may resemble normal pregnancy symptoms; lethargy, tiredness, weight gain, hair loss, dry skin, constipation, fluid retention and goitre.

Discriminating features;

- Cold intolerance
- Bradycardia
- Delayed ankle reflex

Management

- Normal ranges for pregnancy trimesters should be used for assessment, and diagnosed by reduced levels of free T4, T3 and increased TSH.
- Presence of auto-antibodies will help the diagnosis but is not recommended to be performed (anti-thyroid peroxidase antibody) routinely.
- Thyroxine does not freely cross the placenta except for very slight amounts. This will not cause foetal thyrotoxicosis.
- Women who are already on levothyroxine therapy can continue the same dose guided by thyroid function tests (TFT).
- Women who are under replacement therapy need adjustment of dose and TFT should be repeated after 4-6 weeks.
- **Immediate replacement therapy should be started for newly diagnosed hypothyroidism with a starting dose of 100 µg/day. If in case of history of cardiac disease, a lower dose should be introduced.**
- If dose adjustments are made during pregnancy, the dose should be reduced to pre-pregnancy dose after delivery to prevent hyperthyroidism.

Subclinical Hypothyroidism

Include the group of women who do not have symptoms and signs suggestive of thyroid dysfunction and who present with high TSH and normal thyroxine levels. It is common in the presence of anti-thyroid antibodies. Evidence reports improved pregnancy outcome in women supplemented with thyroxine in the presence of anti-thyroid antibodies. However, TSH level between 2.5-4.0 mU/L in asymptomatic patients does not require treatment[5].

Controlled Anti Thyroid Screening trial (CATS) and Maternal-Foetal Medicine Units Networks randomized trials published in 2017 demonstrated no difference in neuro cognitive functions of babies born to mothers with sub clinical hypothyroidism up to the age of 5 in both arms of treatment or no treatment. Recently CATs study in its publication of follow up at 9 years also confirmed no difference in the neurodevelopment of the offspring. However, reading through published trials some have shown higher incidences of preterm birth, abruption, admission to (PBU) premature baby unit, Preeclampsia and gestational diabetes[14,15,16,17]. But some studies have not shown the same results[18,19,20]. **Therefore our conclusion is at present there is no clinical advantage in treatment of subclinical hypothyroidism unless there is the presence of anti-thyroid antibodies of the mother.**

We recommend thyroxine replacement with 25-50 microgram/ day for prenatal women with positive antibodies and subclinical hypothyroidism and titration of TSH to normal levels.

Untreated severe hypothyroidism in the mother can lead to impaired brain development in the foetus. Given ambiguity in outcome of many studies in evaluating pros and cons of treating subclinical hypothyroidism, there is no world-wide consensus of opinion regarding screening all women for hypothyroidism during pregnancy.

General recommendation is to check a woman's TSH as soon as pregnancy is confirmed in women at high risk for thyroid disease, such as those with prior treatment for hyper- or hypothyroidism, a family history of thyroid disease, a personal history of autoimmune disease, and those with a goiter.

Women with established hypothyroidism should have a TSH test as soon as pregnancy is confirmed. They also should immediately increase their levothyroxine dose, because thyroid hormone requirements increase during pregnancy. If new onset hypothyroidism has been detected, the woman should be treated with levothyroxine to normalize her TSH values.

Foetal / Neonatal Hypothyroidism

Occur due to transplacental passage of maternal anti-thyroid antibodies with incidence of 1 in 180,000 pregnancies.

We recommend screening of all neonates with TSH levels via Guthrie Heel Prick Neonatal Screening test.

Postpartum Thyroiditis

Incidence around 1-17% of pregnancies and is more common among women with anti-thyroid peroxidase (anti-TPO) antibodies. It is usually asymptomatic and present around 3-4 months postpartum. It can present as transient hyperthyroidism, transient hypothyroidism or as a biphasic disease (first hyperthyroidism followed by prolonged hypothyroidism). Small, painless goitre can be present in about 50% of women.

Treatment should be guided by symptom control while most recover spontaneously without treatment. 3-4% of women will have permanent hypothyroidism and about 10-25% of women will have recurrence in future pregnancies.

Most women with positive antibodies will develop postpartum depression despite thyroid status.

SLCOG is of the view, that uncomplicated thyroid disease could be managed by the Obstetrics and Gynaecology Consultant with clear knowledge of the disease process.

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