INVITED ARTICLE

# MANAGEMENT OF THYROID DISEASE IN PREGNANCY

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## ABSTRACT

**Thyroid disease occurs in pregnant at the rate of 0.2-0.6%. Graves' disease is the most common thyroid disorder in our pregnant patients. Thyroid disease is suspected if a significant goitre is detected during pregnancy. Confirmation by thyroid function tests is necessary but their interpretation requires an understanding of changes in the maternal thyroid physiology. Pharmacotherapy with the thionamides is the treatment of choice. Changes in dosage are influenced by the effect of pregnancy on the disease and the optimal level of control for the mother and the foetus. The dose is best titrated against the free thyroxine index or free thyroxine level. The outcome of pregnancy depends on early diagnosis and skilful manipulation of antithyroid drugs.**

**Keywords:** Thyroid disease, pregnancy, diagnosis, management

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## INTRODUCTION

The prevalence of hyperthyroidism, mostly from Graves' disease, during pregnancy was estimated at 0.2% and that of hypothyroidism 0.6% (1). Locally, hyperthyroidism is by far the more common clinical thyroid disorder both in and out of pregnancy. The management of thyroid diseases in pregnancy may be somewhat difficult for a number of reasons. Conventional diagnostic tests are confounded by physiological changes of pregnancy and treatment options are constrained by concern for the foetus. To appreciate these factors an understanding of thyroid metabolism in the fetus and mother is necessary.

## MATERNAL-FOETAL THYROID PHYSIOLOGY

The thyroid gland enlarges in pregnancy in association with increased iodine turn-over (1). There is increased iodine loss from the urine and therefore depletion of the total iodine pool. In iodine replete areas where dietary intake is in excess of the new demand, any thyroid enlargement will marginal. Clinically obvious goitre are therefore always suspicious (2, 3). Hyperestrinism in pregnancy induces synthesis of thyroxine binding globulin (TBG).

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Consequently, total thyroxine (TT4) and total triiodothyronine (TT3) are raised by about 50% by the 6th week of pregnancy. The top normal range of TT4 is closer to 12.5 to 15 ug/dl than the usual 12 ug/dl. The free T4 (fT4) and free T3 (fT3) levels were variously reported to be raised, normal or reduced depending on the method of estimation (4). The euthyroid nature of the normal gravid state is demonstrated by a normally responsive hypothalamic-pituitary-thyroid axis. Baseline thyrotropin (TSH) remains within the normal range throughout pregnancy. The TSH response to exogeneous thyrotropin-releasing hormone is similar to the non-gravid state.

The placenta is a natural barrier to maternal TSH and thyroid hormones. Development of the foetal thyroid axis is largely autonomous (5). Foetal TSH and thyroid hormone secretion is evident by the 10-12 week gestation but thyroid function is at basal level till midgestation. Thereafter foetal T4 and T3 increase until term. At the moment of birth a marked surge in TSH secretion is seen which is commonly attributed to body cooling in the external environment. Thyroid hormones rise abruptly especially the metabolically more active T3 by an accelerated hepatic conversion from T4.

## DIAGNOSIS OF THYROID DYSFUNCTION IN PREGNANCY

The clinical diagnosis of hyperthyroidism during pregnancy may be difficult because they are both hypermetabolic states but they differ in that the former is catabolic in nature. The clinical features that favour hyperthyroidism include eye signs, onycholysis, myopathy and weight loss. Hyperemesis gravidarum may be a presenting problem which remits with successful control of the thyrotoxicosis (6). Accurate diagnosis is nevertheless important as severe hyperthyroidism, if untreated, increases maternal morbidity and mortality. It also causes foetal loss, low birth weight and congenital malformation (7). Laboratory data are

necessary to confirm a clinical diagnosis. Total hormone levels are distorted by the raised TBG. The free thyroxine index (FTI) or free T4 (fT4) level are better guides although they are not entirely foolproof. The FTI, a mathematical formula to estimate the free T4 level, usually suffices if changes in the TBG state are small. It is inaccurate for marked changes giving spuriously high readings. The fT4 when used requires correlation with the stage of gestation as reference range changes with the trimesters (4).

## THYROID DISEASES IN PREGNANCY

The most common thyroid disease complicating pregnancy is that of Graves' disease. In the main, these patients conceive as they improve with treatment of their disease. Sometimes we see patients presenting with hyperthyroidism for the first time during pregnancy. It is likely that such patients have mild disease because menstrual irregularity and infertility are common in more severe cases. Occasionally such patients are found to have high human chorionic gonadotrophin level such as in multiple pregnancy and trophoblastic disease (8). Autoimmune thyroid diseases (ATD) tend to ameliorate in severity with the progress of pregnancy. This is in concert with the suppression of maternal immunity to accommodate the antigenically foreign foetoplacental unit. Spontaneous remission of ATD may occur in the latter trimesters associated with decrement in the level of antibodies (anti-thyroglobulin, antimicrosomal or thyroid stimulating anti bodies). A postpartum exacerbation sometimes occurs even if the patient is adequately treated during pregnancy. Indeed ATD presented ror the first time in the postpartum period with fair frequency in certain populations (9-11). Postpartum thyroiditis (PPT) may have an initial phase of hyperthyroidism followed by hypothyroidism before resolving. There is no systematic study of PPT locally. The few cases seen by the authors presented with a goitre. On enquiry, symptoms of hypothyroidism were ellcited.

Thyroid stimulating antibody, being an immunoglobulin, crosses the placenta. If high titres persist in the third semester it could cause foetal or neonatal hyperthyroidism (12). In general such complication is likely if control of maternal Graves' disease has been difficult and indequate. Occasionally, persistence of such antibody after surgery or radioiodine therapy may cause problems despite an apparently euthyroid mother (13). Assay for such antibody may help to elucidate unexplained foetal tachycardia in a mother with history of Graves' disease.

## MANAGEMENT OF THYROID DISEASE IN PREGNANCY

As mentioned previously, hyperthyroidism due to Graves' disease ameliorates with the progress of pregnancy. The pregnant mother tolerates a mild degree of hyperthyroidism remarkably well. Mild hyperthyroidism may thus be left alone but should be monitored. More severe forms should be treated.

Surgery was once an option to be considered at mid-trimester after preparation with anti-thyroid drug. The outcome of successful pregnancy was, however, at times less favourable than pharmacotherapy alone (14).

Surgery is seldom considered now.

## PHARMACOTHERAPY

The thionamides are the mainstay of therapy in gestational hyperthyroidism. Carbimazole (CMZ) passes freely through the placenta and propylthiouracil (PTU) to a lesser extent (15). Their use has been associated with transient low T4 and goitre in the neonates but studies have not shown any long-term problems after such exposure (16, 17). Carbimazole has been associated with aplasia cutis (18) but no teratogenicity has been reported with PTU. The placenta is less pervious to PTU than CMZ for an equally efficacious dose and therefore PTU is preferred in pregnancy.

The starting dose of the thionamides is no different from the non gravid state. Either carbimazole 15-20 mg BD or propylthiouracil 100 mg TDS or QDS is appropriate. Occasionally, larger doses are required but this need not raise the rate of foetal goitre or hypothyroidism since such sequelae are not entirely dose dependent. The increased level in the foetus may in fact preclude foetal hyperthyroidism. Whatever the initial dose, this is then titrated against FTI or fT4 to obtain the top normal or slightly hyperthyroid range. This maternal level is the best in maintaining foetal euthyroidism (19). The maintenance dose is usually in the region of CMZ 5-10 mg or PTU 50-100 mg a day. The precautions and care in the use of thionamides were discussed elsewhere (20).

As mentioned before, the autoimmune state ameliorates with the progress of pregnancy. Indeed after initiation of treatment it may be possible to stop treatment after the second trimester. It is possible that the thionamides contribute to the resolution by their immunomodulating properties (20).

The use of propanolol in pregnancy is associated with small placenta, intrauterine growth retardation, postnatal bradycardia and hypoglycaemia but recent data were less negative (21). It is used in severe cases as a temporary measure.

Both iodine and radioidine therapies are contraindicated in pregnancy. Iodine causes marked obstructive foetal goitre which is life threatening. Radioiodine is taken up with great avidity by the foetal thyroid (20-50 times the normal maternal uptake) leading to hypothyroidism and permanent neurological damage.

The treatment of hypothyroidism is less intricate and does not differ from the non-gravid state. Titration against TSH level will ensure optimal replacement if the TSH is kept at below 5 mu/ml. The replacement dose of L-thyroxine is usually between 50-150 ug a day.

## POSTPARTUM COMPLICATIONS

It is necessary to test the neonate for evidence of congenital hypothyroidism especially if pharmacotherapy is continued into the third trimester. Early diagnosis will prevent seguelae hence cord blood should be obtained for screening (22). Conversely, transfer of maternal immunoglobulin may cause neonatal thyrotoxicosis. This could be delayed for up to 7-10 days because of the residual effect of anti-thyroid drugs. Neonatal thyrotoxicosis may persist for as long as the TSH receptor antibody is present i.e. up to 6 weeks. This complication can be predicted by a high level of thyroid stimulating antibody in the maternal blood. Treatment is required if the disease is severe since the mortality is significant if not treated.

The mother should be warned of possible relapse in the postpartum period (23). If drug treatment is required at this time, she should be cautioned that the thionamides are found in the breast milk. As such breastfeeding is not encouraged. If despite this the mother still wishes to breastfeed then PTU is used since it enters the milk in lesser amounts. Studies thus far did not show abnormal thyroid function if small doses of PTU of 150 mg or less a day are given during lactation (24). Nevertheless, monitoring of the baby's thyroid function is called for.

## CONCLUSION

The management of thyroid disease, especially hyperthyroidism in pregnancy is always challenging. The above approach encapsulates the authors' experience. We have been able to carry out most pregnancies through to term without mishaps and without recourse to surgery. Those which did not succeed suffered losses in the first trimester. Often the patients stopped all treatment with the diagnosis of pregnancy and hence lost control of the hyperthyroidism. It is imperative to inform all potential mothers of the necessary steps to follow, the chief of which is an early review with the attending doctor when pregnancy is suspected. If the management programme discussed is started early a successful outcome is the norm.

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