Thyroid disease in pregnancy

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It has long been known that there is a close relationship between pregnancy and the thyroid gland—iodine insufficiency, goitre development, and abnormal thyroid function are common during pregnancy. Autoimmune thyroid disease and thyrotoxicosis may also affect pregnant women, and their management requires the understanding of the interaction between the neuroendocrine and immune systems. In this article, the physiology of the thyroid gland during pregnancy and the interrelationship between pregnancy and autoimmune thyroid disease are discussed.

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Introduction

Pregnancy poses an important challenge to the maternal thyroid gland as hormone requirements are increased during gestation. Understanding the normal physio-logical adaptation of the pituitary-thyroidal axis in pregnancy enables us to manage cases of thyroid dysfunction. Autoimmune thyroid disease usually affects females of the reproductive age group and caring for these women during pregnancy requires careful monitoring of both the mother and the foetus. This review summarises the physiological adaptation of the thyroid gland and the management of thyroid disease during pregnancy.

Thyroid function in pregnancy

Increased hormone requirements

In response to stimulation by oestrogen, serum thyroxine binding globulin (TBG) levels rise from the first trimester until 6 to 12 months postpartum.[1] This results in a raised total thyroxine level (TT_4) in all pregnant women but a normal free thyroxine level (FT_4) and free thyroxine index (FTI). In order to maintain stable free hormone levels, the feedback mechanism stimulates thyroid stimulating hormone (TSH) release which acts to increase hormonal output and re-establish the homeostasis of free hormone levels. An adequate adjustment by the thyroid gland therefore requires that the thyroid's functional capacity be able to meet this extra demand.

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Increased iodine requirement

During pregnancy, additional iodine is lost through the increased renal clearance of iodide.[2] This loss is further aggravated during the second half of gestation because a fraction of the maternal inorganic iodide pool is diverted towards the foetal-placental complex, thereby further depriving the maternal thyroid from available iodine. It has been shown that in areas of borderline iodine intake, goitre develops with relative hypothyroxinaemia, higher T_3/T_4 ratios indicate preferential T_3 secretion, and higher, although normal, serum TSH concentrations arise.[3] Thus in places of borderline iodine intake, iodine supplementation is needed during pregnancy to prevent relative maternal hypothyroxinaemia and goitre development.[4] As Hong Kong is one of the few place in Southeast Asia where the salt is not iodized,[5] iodine supplementation can be achieved by prescribing multivitamin pills that contain potassium iodide.

Effect of human chorionic gonadotropin

Human chorionic gonadotropin (hCG) is produced in large quantities during pregnancy, particularly at the end of the first trimester. Because of its molecular similarities with TSH, hCG acts as a weak thyrotropic hormone and stimulates the maternal thyroid gland to enlarge and increase its hormone production.[6] In the vast majority of healthy subjects, the stimulatory effect of hCG on the thyroid gland is negligible, of short duration, and without clinically detectable consequences. However, in those with abnormally elevated and sustained levels of hCG and associated hyperemesis gravidarum, serum FT_4 may become supranormal and the TSH level may be suppressed. These subjects may also present with thyrotoxic symptoms including weight loss, vomiting, and

tachycardia. It is thus important to be aware that thyrotoxicosis of non-autoimmune origin may occur during the first trimester of pregnancy. At times, however, it may be difficult to distinguish these subjects from those presenting with Graves' disease in the first trimester. The use of erythrocyte zinc measurement may be helpful in distinguishing pre-existing Graves' disease from hCG-induced thyrotoxicosis. Patients with pre-existing hyperthyroidism may have low erythrocyte zinc concentrations, whereas those with transient biochemical hyperthyroid induced by hCG usually have normal zinc levels.[7] As most cases of hCG-induced hyperthyroxinaemia are transient, the thyroid function tests usually return to normal by the second trimester without treatment. However, in those women with persistent hyperemesis and hyperthyroxinaemia in the second half of pregnancy, antithyroid drug therapy should be considered.

Graves' disease during pregnancy

Disease activity

During the first trimester, there may be an exacerbation of hyperthyroidism due to the stimulatory effect of hCG. However, the clinical condition usually diminishes during the second and third trimester as a result of a generalised reduction of the cellular immune response of the mother to accommodate the histoincompatible foeto-placental unit. During the postpartum period, about 50% of women have a relapse of their Graves' disease and this usually occurs 6 to 12 months after delivery.

Complications

Uncontrolled thyrotoxicosis is associated with a higher incidence of spontaneous abortion and foetal abnormality rate.[8] It is thus prudent to control thyrotoxicosis and render the patient biochemically euthyroid before advising pregnancy. However, there is no contraindication to pregnancy in women receiving antithyroid drugs.

Treatment

The mainstay of treatment is antithyroid drugs. Propylthiouracil is the preferred agent as methimazole is associated with the complication of aplasia cutis in the foetus. However, as this complication is very rare and relatively benign, it may not be necessary to change over to propylthiouracil in a woman who is stable on methimazole upon confirmation of the pregnancy.[9] Again, propylthiouracil is preferred in the lactating mother as it enters the breast milk to a lesser extent than do carbimazole and methimazole. The aim of treatment is to use the lowest dose of antithyroid drugs to maintain euthyroidism and to keep the FT_4 level or FTI in the upper range of normal to avoid foetal hypothyroidism and goitre formation. The use of a block replacement regimen consisting of a large dose of antithyroid drug plus a thyroxine supplement is not advisable. If the thyrotoxicosis is mild, the antithyroid drugs can usually be withdrawn about four weeks before delivery without complications. The usual maintenance dose is carbimazole 5 mg daily or propylthiouracil 50 mg daily.

Beta-blockers are indicated if the mother is severely toxic. However, their use during the third trimester is associated with intrauterine growth retardation, a small placenta, postnatal bradycardia, and foetal hypoglycaemia. Hence, it is advisable to limit its use to a short time and to withdraw the drug once the woman is clinically euthyroid.

Surgery is reserved for those who cannot tolerate anti-thyroid drugs due to a sensitivity reaction or to poor drug compliance. The patient must be euthyroid before the operation, which preferably should be performed during the second trimester. If the patient is sensitive to both carbimazole and propylthiouracil, adequate control of symptoms and pulse rate can be achieved by using a large dose of β-blocker before surgery. Radioactive iodine is absolutely contraindicated in pregnancy as well as the 6 months preceding conception.

Maternal and foetal monitoring

As all pregnant women have raised TBG levels, the serum TT_4 level cannot distinguish thyrotoxicosis from euthyroidism. Monitoring of maternal thyroid function requires either the serum FT_4 level or an FTI. Some of the commercial FT_4 two-step analogue assays may give spuriously low readings during the last trimester of pregnancy due to assay interference.[10,11] In doubtful cases, a serum FTI may provide a better reflection of the true thyroid status of the woman. During treatment with anti-thyroid drugs, one should also monitor the foetal heart rate, and if possible, perform ultrasound assessment of foetal growth and goitre size for evidence of foetal hyperthyroidism or hypothyroidism.

Labour and delivery

The major obstetric risk for women with uncontrolled Graves' disease is the onset of premature labour. This complication is uncommon if the hyperthyroidism is adequately controlled. In premature infants with congenital Graves' disease, lung maturation is accelerated along with skeletal development, and the respiratory distress syndrome is rare. Thyroid storm is an infre-

quent complication during labour or delivery unless the diagnosis of Graves' disease has not been suspected, or the patient has superimposed infection or surgical stress. Management of this problem is the same as in nonpregnant women, except that caesarean section may be required because of foetal distress.

Neonatal complications

Neonatal thyrotoxicosis is probably due to the transplacental transfer of TSH receptor stimulating antibodies.[12] This is a rare condition especially if the mother is adequately treated. Its presence should be suspected if the foetus has persistent tachycardia of greater than 160 beats per minute. The clinical presentation of neonatal thyrotoxicosis may be delayed until 7 to 10 days after birth. Thus, it is important to look for signs of hyperthyroidism, exophthalmos, and goitre at birth and up to 2 months of life, at which time maternal immunoglobulin should have been metabolised. Serum from cord blood should be assayed for both FT_4 and TSH, and if possible, TSH receptor stimulating antibodies as well. Neonatal hypothyroidism can be caused by the transplacental transfer of antithyroid drugs. Consequently, it is important to use the minimum dose of antithyroid drugs to control maternal hyperthyroidism. Neonatal hypothyroidism, transient or permanent, can also be caused by the transplacental transfer of blocking types of TSH receptor antibodies that may be present in patients with Graves' disease or Hashimoto's thyroiditis.[13,14]

Postpartum thyroiditis

Although there are no local data, postpartum thyroiditis has been reported to occur in 5% to 18% of healthy pregnant women in different populations.[15] These women have transient hyperthyroidism or hypothyroidism occurring 3 to 6 months after delivery that is associated with the development of a small, painless goitre. Circulating microsomal and/or thyroglobulin antibodies are usually present. This condition is due to a self-limiting lymphocytic thyroiditis and can be distinguished from Graves' disease by a low thyroid uptake of radioiodine. More than 90% of patients recover completely but the condition may recur during a second pregnancy. It should be noted that patients with postpartum hypothyroidism may present with postpartum depression.

Hypothyroidism in pregnancy

As explained, hormonal requirements increase during pregnancy. Hence, patients with hypothyroidism who are receiving thyroxine replacement may require a 40% to 50% increase in their daily T_4 dosage to maintain euthyroidism.[16,17] Those with subclinical hypothyroidism may become biochemically hypothyroid and require thyroxine replacement. The aim of control is to achieve normal serum concentrations of both FT_4 and TSH.

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