REVIEW ARTICLE

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Drug Therapy for Hyperthyroidism in Pregnancy

Safety Issues for Mother and Fetus

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Abstract

Hyperthyroidism (thyrotoxicosis) in pregnancy and the child bearing years is usually attributable to Graves' disease. This is an autoimmune condition in which thyroid-stimulating immunoglobulins (TSI) cause hyperthyroidism. As a rule, pregnancy complicates the management of hyperthyroidism, rather than vice versa. However, patients who remain thyrotoxic during pregnancy are at increased risk of maternal and fetal complications, particularly miscarriage and stillbirth. Therefore, bodyweight loss, eye signs and a bruit over the thyroid gland in a pregnant

woman warrant thyroid investigation. Investigations should include measurement of serum free thyroid hormone levels [free thyroxine (T_4) and free triiodothyronine (T_3)] rather than total T_4 and T_3 levels, because total T_4 and T_3 levels may be raised in euthyroid pregnancies due to the presence of increased levels of thyroxine binding globulin (TBG).

By 20 weeks' gestational age, the fetal thyroid is fully responsive to TSI and to antithyroid drugs. Maternal T_4 and T_3 and thyrotropin pass across the placenta in small and decreasing amounts as gestation progresses, but thyrotropin releasing hormone, TSI, antithyroid drugs, iodides and β-blockers are readily transferred to the fetus from the mother.

Hyperthyroidism is usually treated throughout pregnancy with an antithyroid drug, preferably propylthiouracil. The smallest dose which controls the disease is given with careful monitoring of free T_4 and T_3 levels to minimise the risk of fetal hypothyroidism and goitre. Bilateral subtotal thyroidectomy may be an option for a small number of patients with hyperthyroidism in pregnancy.

Hyperthyroidism (thyrotoxicosis) is seen in 0.1 to 0.2% of pregnancies.[1-4] Graves' disease is the most common cause of hyperthyroidism in the childbearing years[5] and in pregnancy.[6] This autoimmune disease is caused by the presence of thyroid-stimulating immunoglobulin (TSI). Less common causes of hyperthyroidism are toxic solitary nodule, toxic multinodular goitre, hyperemesis gravidarum and trophoblastic disease in pregnancy, and painless thyroiditis in the postpartum period.

Both hyperthyroidism and hypothyroidism have been regarded as a cause of infertility[7,8] but only severe thyroid dysfunction is now thought to be important in this regard.[6] Nonetheless, thyrotoxic patients often present with infertility[7,8] and become pregnant after tretment with antithyroid agents is started.[6]

Thyroid hormones are essential to normal development and function of nearly all organ systems, especially the CNS.[9] Normal thyroid function is shown in figure 1.

Iodine is necessary for the synthesis of thyroid hormone. It is absorbed from the small bowel and actively taken up by the thyroid gland where it is oxidised and incorporated into tyrosine residues of thyroglobulin to form mono and diiodotyrosines. These are coupled to form triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). In hyperthyroidism, all phases of iodine metabolism are increased. In pregnancy, iodine uptake is increased but so also is renal iodide clearance. This can lead to relative iodide deficiency in pregnant women who live in areas where dietary iodide is low.[10]

From the fourth to the sixth week through pregnancy, maternal serum thyroxine binding globulin (TBG) is increased due to estrogen stimulation of its hepatic synthesis.[11] In addition, sialylation of TBG is increased and this slows its clearance.[12] Consequently, serum total T_4 is raised but serum free T_4 remains within the euthyroid range during pregnancy. Serum levels of T_4, free T_4, total T_3 and free T_3 rise to the high/normal range in early pregnancy but fall to low/normal in the last trimester. The early rise is probably attributable to the thyrotropin (thyroid stimulating hormone)- like effect of human chorionic gonadotrophin (hCG), as serum thyrotropin level is then normal or low. Serum thyrotropin level rises through pregnancy as serum free T_4 and T_3 levels fall. Details in reports on maternal thyroid function vary but the data in table I is indicative of the changes.[11]

Sensitive thyrotropin measurement and free T_4 and T_3 levels are used to assess thyroid function in pregnancy. Hyperthyroidism is confirmed when thyrotropin levels are low and free T_4 and free T_3 levels are high. Rarely, only free T_3 levels are increased.[13] Graves' disease can usually be diagnosed on clinical grounds, but is confirmed by detection of thyroid microsomal antibodies and TSI.

An ultrasound scan may be useful to document

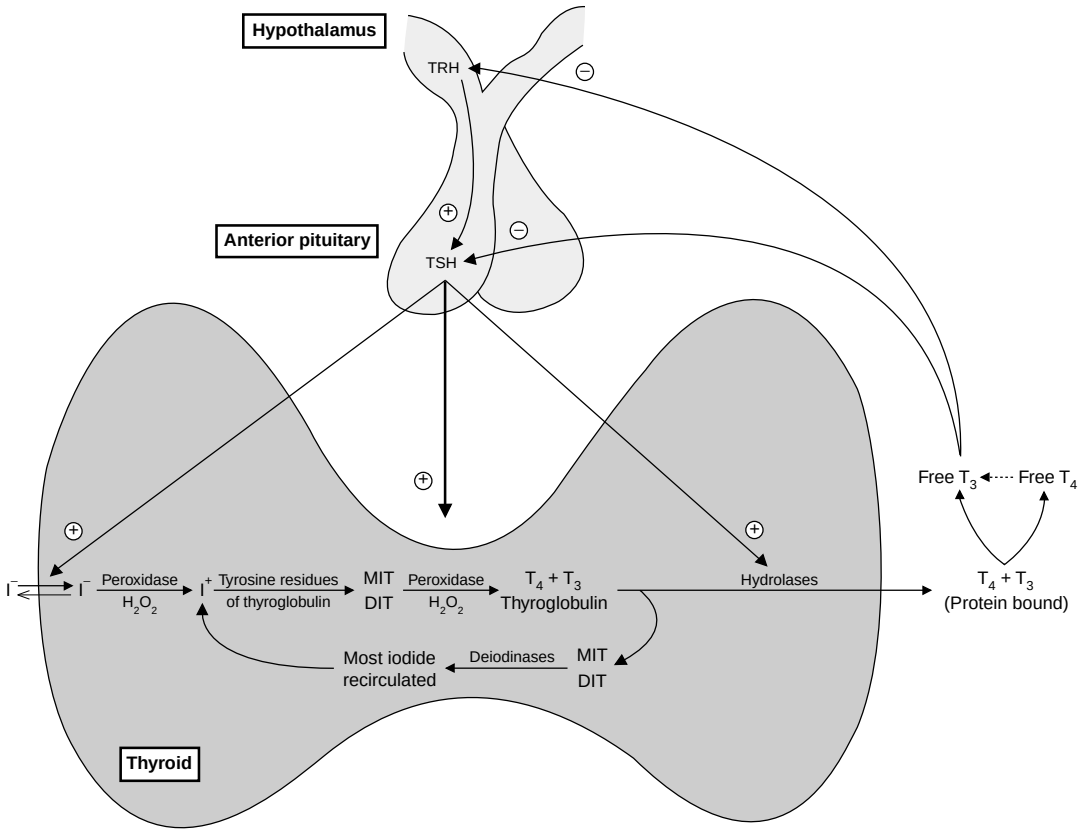

Fig. 1 Simplified representation of the normal regulation of thyroid function. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates thyrotropin (TSH) release from the anterior pituitary. TSH stimulates iodide transport, synthesis and release of thyroid hormones. The intrathyroid iodide content also influences iodide uptake. On release, most thyroid hormone is bound by plasma proteins e.g. thyroxine binding globulin. Only free hormone is metabolically active. Free triiodothyronine (T_3) provides a negative feedback inhibiting production and secretion of TSH and inhibiting the effect of TRH. **DIT** = diiodotyrosine; **MIT** = monoiodotyrosine; **T_4** = thyroxine (tetraiodothyronine); **+** = stimulation; **-** = inhibition.

thyroid size and reveal nodularity in patients with suspected Graves' disease. Although the fetal thyroid is not developed before 10 weeks, radioactive isotope tests should be avoided throughout pregnancy.

1. Hyperthyroidism in Pregnancy

1.1 Effects on the Mother

Maternal heart failure may occur in untreated or inadequately controlled hyperthyroidism.[1,14] Reports suggest that the maternal mortality rate is not increased unless pre-eclampsia supervenes.[15] Fortunately, thyrotoxic crisis is extremely rare in pregnancy. However, when it does occur, this condition is most likely to occur during delivery, with eclampsia or in the postpartum period.[16,17]

Concurrent diabetes mellitus becomes more difficult to control in pregnant women with hyperthyroidism.[18]

1.2 Effects on the Pregnancy

Unrecognised or inadequately treated hyperthyroidism can have very serious effects on the course

Table I. Thyroid function in normal pregancy

Trimester	TBG	Thyrotropin	Total T_4	Free T_4	Total T_3	Free T_3
First	Increased	Low/normal	High/normal	High/normal	High/normal	High/normal
Second	Increased	Normal	High/normal	Normal	High/normal	Normal
Third	Increased	High/normal	Low/normal	Low/Normal	Low/normal	Low/normal

TBG = thyroxine binding globulin; **T_4** = thyroxine (tetraiodothyronine); **T_3** = triiodothyronine.

of pregnancy.[1,19] A review of 120 000 pregnancies showed that 60 were complicated by overt hyperthyroidism. With diagnosis before pregnancy and earlier treatment, 80% were euthyroid at delivery. Those diagnosed during pregnancy had a higher rate of morbidity, stillbirths, relative delay in gestational age at diagnosis, preterm delivery and perinatal mortality.[1] Similarly, Montoro and Mestman[20] recorded 15 premature deliveries, 5 perinatal deaths and 5 cases of neonatal morbidity out of 19 patients with untreated hyperthyroidism.

1.3 Effects of Hyperthyroidism on the Fetus and Neonate

Normally, the fetal hypothalamic-pituitary-thyroid axis begins to function at 10 weeks' gestational age as the thyroid starts to concentrate iodine. At 12 weeks, T_4 is secreted by the thyroid and thyrotropin, by the pituitary.[21] Fetal T_4, TBG, free T_4 and thyrotropin levels increase progressively through pregnancy; levels of thyrotropin are higher in the fetus than in the mother. Fetal T_3 and free T_3 levels are very low in early pregnancy but increase from the thirtieth week of gestation (Table II).[22]

The placenta is a significant barrier to the transfer of maternal thyrotropin, T_4 and T_3 to the fetus.[3,23] On the other hand, thyrotropin releasing hormone (TRH) and TSI in Graves' disease readily cross the placenta. That the placenta is not a total barrier to maternal T_4 and T_3 was shown by the finding of T_4 and T_3 in a neonate with thyroid agenesis.[24] In Graves' disease, TSI cross the placenta and may cause intrauterine and neonatal hyperthyroidism. The level of TSI in the mother is correlated with the risk of these complications. Neonatal hyperthyroidism is usually transient, but has been reported in 1 in 70 births to mothers with hyperthyroidism.[15] The reported incidence of neonatal hyperthyroidism in this setting ranges from 1 to 10%.[6,25]

In 1984 it was suggested that congenital anomalies were increased in infants of mothers with untreated or inadequately treated hyperthyroidism,[14] but this was not confirmed by later reports.[26,27]

Antithyroid agents iodine and β-blockers such as propranolol also cross the placenta.[28-30] The fetal thyroid gland becomes fully responsive to antithyroid drugs by 20 weeks' gestational age.[3]

The placenta and mammary gland accumulate iodide and this may be important in providing adequate supplies of iodide for fetal and infant thyroid hormone synthesis.

1.4 Effects of Pregnancy on Hyperthyroidism

The increased protein binding of thyroid hormones and immunosuppression seen in pregnancy both have a beneficial effect in that Graves' disease has a tendency to remit, although postpartum relapse is common.[3,19,31,32]

2. Choice of Management

In the nonpregnant patient of childbearing years, there is a strong argument for definitive treatment rather than prolonged and repeated courses of antithyroid drugs. This may be either by radioactive iodine as commonly favoured in the US, or by surgery, which is often preferred in the UK.[33-35] In the US, it is usual to advise women to avoid pregnancy for a minimum of 3 months after radioactive iodine therapy.[36] In the UK, a delay of 4 months is advocated.[37] This interval has also been applied to prospective fathers who receive radioactive iodine therapy.[38]

Radioactive iodine is completely contraindicated in pregnancy. Antithyroid drugs are generally used

during pregnancy[6] but subtotal bilateral thyroidectomy may be an option for some patients.[39-42] The older literature suggests that surgery has wide application for hyperthyroidism in pregnancy,[43,44] but this approach is now seen as having a more limited role. There have been no prospective randomised trials comparing medical with surgical treatment. However, one review of the literature, which was based on 318 women treated with antithyroid drugs and 288 treated surgically, concluded that there was no apparent advantage for one form of treatment over the other.[45]

Adverse effects of antithyroid drugs and an inability to control the disease on low doses of these agents are now the most common indications for surgery. Reed Larsen et al.[7] believe that in compliant patients, a propylthiouracil requirement of more than 400 mg/day is a reasonable threshold for considering subtotal thyroidectomy, preferably in the second trimester.[7] Lower threshold doses have also been advocated, e.g. propylthiouracil 300 mg/day or carbimazole 10 mg/day.[15,42] Less common indications for surgery now are patients who present with severe hyperthyroidism, have a long history of the disease or a large gland. An additional but unusual indication for surgery is an anxious mother who fears the effects of medication on the fetus and will not adhere to an antithyroid drug regimen.

Antithyroid drugs are used in early pregnancy in all patients with hyperthyroidism provided that they are tolerated without adverse reactions. As the middle trimester approaches, a decision on further management either by continued antithyroid medication or surgery must be made. This requires careful discussion with both the patient and the obstetrician. It has been argued that surgery should not be performed until the fetus is viable in case this intervention results in early delivery.[36] However, it is generally accepted that surgery is best undertaken in the middle trimester, when the risk of miscarriage is at its lowest. Unfortunately, a decision about surgery has to be made before there is a chance to see whether there is amelioration of the patient's hyperthyroidism during the third trimester.

3. Antithyroid Drugs

Astwood[46] successfully treated 3 patients with thiourea and thiouracil in 1943. Subsequently, safer drugs such as methylthiouracil and propylthiouracil were introduced to clinical practice, and were followed by thiol compounds such as thiamazole (methimazole) and its carbethoxy derivative, carbimazole. The most commonly used antithyroid drugs are carbimazole in Europe, and thiamazole and propylthiouracil in the US.[33]

3.1 Modes of Action

The effects and doses of carbimazole and thiamazole are similar, because carbimazole is almost completely converted to its active metabolite thiamazole, by hydrolysis and decarboxylation *in vivo*.[47]

Thiamazole and propylthiouracil reduce synthesis of thyroid hormones. These drugs are concentrated by cells with a peroxidase system. By inhibiting thyroid peroxidase they interfere with the incorporation of oxidised iodide into tyrosine residues in thyroglobulin. They also block the coupling reaction in

Table II. Thyroid function in the normal fetus

Gestational age (wk)	Iodine	TBG	Thyrotropin	Total T_4	Free T_4	Total T_3	Free T_3
10-12	Concentration of iodine begins		Secretion starts	Secretion starts			
20-30	Thyroid fully responsive	High	Progressive increase	Progressive increase	Progressive increase	Low	Low
30-40		High	High	High	High	Progressive increase	Progressive increase

TBG = thyroxine binding globulinl; **T_3** = triiodothyronine; **T_4** = thyroxine (tetraiodothyronine).

which mono and diiodotyrosines are linked to form T_4 and T_3.[3,4,48,49]

Propylthiouracil but not thiamazole also interferes with the peripheral conversion of T_4 to T_3 by inhibiting type 1 deiodinase. Antithyroid drugs may also cause a gradual reduction in the level of TSI, resulting in an increase in suppressor T cell activity.[50]

The serum half-life of propylthiouracil (75 minutes) is considerably shorter than that of thiamazole (4 to 6 hours).[9,51] Both drugs persist in the thyroid gland for much longer than this and have a prolonged effect on thyroid function.

3.2 Risks to the Mother

The adverse effects of carbimazole, thiamazole and propylthiouracil to the mother are similar. The most common adverse effect associated with these drugs is mild leucopenia (white blood cell count <4000/mm^3) in 12% of patients,[52] but leucopenia also occurs in patients with untreated hyperthyroidism.[53] Leucopenia is usually transient in patients who receive antithyroid drugs. Agranulocytosis, though rare, is the most important adverse effect of antithyroid drug therapy. It occurs in 0.2% of patients and was previously thought to be more likely to occur in patients aged >40 years and in those receiving high doses of carbimazole or thiamazole.[52,54] More recently, it has been stated that agranulocy the dose, duration or previous history of antithyroid drug therapy.[53] The onset of this adverse effect is usually rapid. Unfortunately, monitoring white blood cell count during treatment has no predictive value. Patients should be given instructions, ideally with a written reminder, to immediately report any experience of sore throat, mouth ulcers, bruising, malaise or other clinical features of infection, which could indicate agranulocytosis. Antithyroid drug therapy should be discontinued immediately, white blood cell count should be carefully monitored and a throat swab and blood culture should be done. Appropriate antibacterial therapy is necessary if there is evidence of infection.

Minor adverse effects occur in 5% of patients who receive antithyroid drugs. These include maculopapular rash, pruritus, nausea and vomiting, and usually occur in the first 2 months of treatment. Less common adverse effects include fever, headache, arthralgia, alopecia and taste disturbance. Cholestatic jaundice has been reported in patients who received carbimazole or thiamazole. Vasculitis, systemic lupus erythematosus and a haemorrhagic tendency have been reported rarely in patients who received propylthiouracil. These adverse effects may have an underlying immunological mechanism and cross-sensitivity between these drugs occurs, although this is rare. Usually, propylthiouracil can be substituted for carbimazole or thiamazole and vice versa.[3,4,9,51]

3.3 Risks to the Fetus and Neonate

Concerns for the fetus have centred on the possibilities that malformations could occur if antithyroid drugs are given during the first trimester and impairment of growth and functional development could occur if these drugs are administered during the second and third trimesters.

3.3.1 Malformation

There is little evidence to suggest that antithyroid drugs are associated with congenital malformations. The risk of malformation was reported to be 6% in 643 neonates born to mothers with untreated hyperthyroidism in the first trimester, compared with only 1% where the mothers became euthyroid when treated with thiamazole.[14] In a recent study, congenital malformations were reported in 3% of neonates whose mothers received propylthiouracil, and in 2.7% of those whose mothers received thiamazole. These figures are similar to the reported rates of spontaneous congenital malformations in the general population (2 to 5%).[27]

Another report showed that the risk for birth defects in pregnant women with thyroid disease was similar with or without treatment in a population-based, case-controlled study.[26]

Aplasia cutis has been described as a complication of thiamazole[55,56] but subsequent reports have failed to confirm this. This adverse event has not been associated with propylthiouracil. In a review of a 27 year period where none of the mothers had been receiving antithyroid drugs, the incidence of

congenital skin defects was 0.05% and even less (0.03%) where confined to the scalp. No skin defects were seen in 24 neonates whose mothers had been receiving antithyroid drugs. The risk for congenital scalp defects was not significantly increased in neonates born to mothers treated with thiamazole or its analogue carbinazole.[57]

Momotani et al.[14] failed to demonstrate skin defects in 243 neonates of mothers treated with thiamazole.

3.3.2 Growth and Functional Development – Fetal and Neonatal Hypothyroidism

The risk posed to the fetus by antithyroid drugs is of hypothyroidism and goitre.

Maternal doses of propylthiouracil as low as 100 to 200mg may cause transient fetal hypothyroidism. In 11 neonates born to mothers who received antithyroid drugs during pregnancy, the mean T_4 level was slightly lower and mean thyrotropin level was slightly higher than in neonates from normal pregnancies.[58]

In one report in mothers with hyperthyroidism who received antithyroid drugs during pregnancy, T_4 levels were essentially identical in cord and maternal blood in 27 women in whom it was possible to discontinue antithyroid drugs prior to delivery. However, in 43 mothers in whom the drug was continued to delivery, T_4 levels in cord blood were slightly lower than maternal levels. T_4 levels were lower or thyrotropin levels were higher in cord compared with maternal blood, or both in 54% of mothers who were euthyroid while receiving antithyroid drugs.[59]

About 1% of neonates have significant transient hypothyroidism and a small goitre may be present when the mother is treated with antithyroid drugs.[3] The presence of a goitre, although related to fetal hypothyroidism, bears little relation to the dose of antithyroid drug given to the mother.[3,4]

3.4 Effect on Childhood Development

Thyroid hormone is essential for brain development. Reassurance about long term effects of antithyroid drugs has been provided for both propylthiouracil and thiamazole. Children of mothers treated in pregnancy with propylthiouracil were followed for 10.5 years, and showed no evidence of delayed physical or mental development. Childhood and adolescent intellectual development appeared to be unimpaired.[60] Similar conclusions were reached with regard to the long term effects of carbimazole.[61] Messer et al.[62] reported that long term surveillance of the effects of maternal antithyroid drug therapy on the somatic and intellectual development of children failed to demonstrate any detrimental effects.[62]

4. Which Antithyroid Drug Regimen to Use in Pregnancy?

Both thiamazole and propylthiouracil are effective drugs[47] with comparable fetal outcomes.[27] In the nonpregnant patient, carbimazole and thiamazole have advantages over propylthiouracil. There are fewer major adverse events associated with the first 2 antithyroid drugs, including agranulocytosis, but there are more minor adverse events.[54] Compliance may be better with carbimazole and thiamazole as they can be taken once per day compared with 2 to 3 times per day for propylthiouracil. Reportedly, there is less 'aftertaste' with thiamazole. Compared with propylthiouracil, carbimazole is cheaper in the UK and thiamazole was cheaper in the US.[51] In pregnancy and during breast feeding, the balance is in favour of propylthiouracil. Although propylthiouracil, carbimazole and thiamazole cross the placenta and affect fetal thyroid function, the greater protein binding, poorer solubility in aqueous solutions and ionisation at pH 7.4 of propylthiouracil have generally been thought to reduce the amount passing to the fetal thyroid[29,63] or into breast milk.[64] It has been reported that propylthiouracil crosses the placenta at about a quarter of the rate of thiamazole, and propylthiouracil partially inhibits the peripheral conversion of T_4 to T_3.[19,29,49,63] *In vitro* perfusion of human full-term placenta lobule with low and high doses of thiamazole and propylthiouracil failed to confirm the generally accepted difference in placental transfer of the 2 drugs.[65]

Earlier concerns that aplasia cutis could be associated with antithyroid drugs related only to carbimazole and thiamazole and not to propylthiouracil.[55,56]

A number of factors influence the rapidity with which a hyperthyroid patient treated with antithyroid drugs reaches a euthyroid state. Patients with large and nodular goitres are, in general, slower in their response than those with small, diffuse glands. The quantity of stored thyroid hormone, rate of turnover in the thyroid, the half-life of thyroid hormone in the periphery and the completeness of the block all have an influence.[9,66]

Although the difference was not statistically significant, the free T_4 index was normalised by 7 weeks with propylthiouracil compared with by 8 weeks with thiamazole in pregnant women with hyperthyroidism.[27] In nonpregnant patients with hyperthyroidism, the reverse was shown.[67]

In the nonpregnant patient with hyperthyroidism, a variety of regimens have been utilised in an attempt to lengthen periods of remission, but none has been generally accepted. Regimens have involved large doses of antithyroid drug,[68-72] combination of antithyroid drug with T_4,[73-75] variation of the duration of treatment[76,77] and continuing T_4 administration after discontinuation of antithyroid drugs.[73] Population differences may be the reason for striking differences in reported results.

Hashizume et al.[78] reported a study in which they stopped antithyroid drug treatment at 5 to 6 months of pregnancy but continued treatment with thyroxine. The relapse rate at 1 year postpartum was 5% compared with 32% in those not given thyroxine. This was not a block and replacement regimen where antithyroid drug and thyroxine are given concurrently. Such a regimen should not be used during pregnancy as the fetus is then exposed to high doses of antithyroid drug without being able to benefit from the prescribed thyroxine.

A review of outcomes from 20 reports of hyperthyroidism in pregnancy compared antithyroid drug therapy alone with antithyroid drug therapy combined with T_4. This showed that the rates of fetal loss (14 and 9%) and the percentages of offspring with cretinism or hyperthyroidism did not differ significantly between the 2 treatment regimens. However, congenital abnormalities were significantly more common when the combination regimen was used.[79]

Propylthiouracil is the drug of choice and is prescribed in an initial dosage of 100 to 150mg 3 times per day; the dose is reduced as quickly as clinical control of hyperthyroidism and return of free T_4 levels to the high normal range allows. The patient with hyperthyroidism who is receiving carbimazole or thiamazole and who becomes pregnant can continue to receive the same drug. Careful titration of the dose should be continued throughout pregnancy, based on free T_4 levels in euthyroid pregnant women. In pregnant women with Graves' disease, the fetal and maternal thyroid glands are under the same stimulatory and inhibitory factors, thus control of maternal hyperthyroidism may cause fetal hypothyroidism. Maternal serum T_4 level is reported to be useful, and certainly it, or preferably free T_4, is the most practical indicator of fetal thyroid function.[59] It should be recalled that fetal hypothyroidism can occur even when maternal serum T_4 levels are in the normal range. Therefore, the mother's serum T_4 level should be maintained in the high normal range. It may be possible to reduce the dose of antithyroid drug in the last month of pregnancy,[3,59] but although it is often recommended that the drug should be stopped in the last 6 to 8 weeks this may be possible in only 28% of cases and in some an increase in dose becomes necessary.[80] If it is possible to discontinue the antithyroid drugs, hyperthyroidism recurs in 50% post partum.[6]

Ultrasound examinations through pregnancy are helpful in showing fetal growth, heart rate and possible development of a fetal goitre.[81] A fetus which is small for its gestational age and with tachycardia >160 suggests fetal hyperthyroidism and this may be accompanied by a goitre. High levels of TSI during late pregnancy is a warning sign for fetal and neonatal hyperthyroidism.[82] The neonate must be carefully examined; some clinicians recommend that cord blood be taken to determine fetal thyroid function.[81] However, normal or near normal cord blood thyrotropin and T_4 levels do not

exclude later development of neonatal hyperthyroidism. This condition may present at birth or be delayed until 8 to 9 days after birth. The delay is due to carryover of maternal antithyroid drug and possibly thyrotropin receptor blocking antibody. The neonate may exhibit goitre; central nervous system signs such as irritability, jitteriness and restlessness; eye signs such as oedema, lid retraction and proptosis; cardiovascular signs such as tachycardia and arrhythmias leading to cardiac failure; and general signs of hypermetabolism including persistent acrocyanosis, increased appetite, weight loss, diarrhoea, sweating and flushing. Although it may be self-limiting, neonatal hyperthyroidism has a high mortality rate and should be anticipated and prevented.[83] In most pregnancies fetal hyperthyroidism is effectively prevented by control of the mother's hyperthyroidism. However, the neonate with hyperthyroidism should receive propylthiouracil 5 to 10 mg/kg/day or carbimazole 0.5 to 1 mg/kg/day. Both drugs should be administered in divided doses and should be withdrawn only after several weeks of careful monitoring. If immediate treatment of the neonate is not required close observation for signs of the condition must continue for at least 2 weeks.[83] Neonatal hyperthyroidism may also occur in infants born to mothers who are euthyroid but have had previous successful treatment of Graves' disease, or who have Hashimoto's disease.[15]

Neonatal hypothyroidism is uncommon when the mother's hyperthyroidism has been carefully controlled, but requires prompt assessment and treatment when it does occur. Routine screening in the UK is with a heel prick thyrotropin assay, but when hypothyroidism is suspected, neonatal serum T_4 levels should be measured. T_3 levels are variable.[83] Neonatal serum T_4 and thyrotropin levels should be repeated at 3 days as by then transient hypothyroidism due to carryover of maternal antithyroid drug therapy will usually have resolved.[59] Adequate treatment of neonatal hypothyroidism is initially with oral T_4 8 to 10 μg/kg/day and usually results in normal growth and development.[6]

A mother who is receiving propylthiouracil, carbimazole or thiamazole can breastfeed. The proportion of maternal antithyroid drug ingested by the baby has been calculated as 0.07% of the administered dose of propylthiouracil, compared with 0.5% and 10% of the administered doses of carbimazole and thiamazole, respectively.[38] Ideally a mother who is breastfeeding should receive the lowest effective dosage of propylthiouracil. With low dosage the infant's thyroid function appears to be unaffected. Nonetheless, the neonate's development and thyroid function should be carefully monitored.

5. Other Drugs Used in Thyrotoxicosis and Thyrotoxic Crisis

β-blockers such as propranolol and iodide are commonly used in treatment of hyperthyroidism, but should be avoided in pregnancy as far as possible.

5.1 Propranolol

Successful use of propranolol throughout pregnancy for both hypertension and hyperthyroidism was noted in early reports. This allowed postponement of definitive treatment of hyperthyroidism in pregnancy.[84,85] Subsequently, intrauterine growth retardation, small placenta, hypoglycaemia, hypocalcaemia, fetal bradycardia and neonatal respiratory depression and low Apgar scores were associated with propranolol therapy in pregnancy.[86,87] Difficulties appeared to be most marked when the drug was administered in late pregnancy. Fetal bradycardia indicative of fetal distress may be particularly confusing.[88] Campbell[89] raised the possibility of a teratogenic effect in an infant born with a type A tracheo-oesophageal fistula but this has not been confirmed.

A more sanguine view of β-blockers used in the management of hypertension in pregnancy has also been reported.[90]

During pregnancy, short courses of propranolol are used to treat tachycardia or to control thyrotoxic crisis. In practice, many physicians also use propranolol in low doses as an adjuvant to antithyroid drugs without experiencing problems.

5.2 Iodine

Iodides cross the placenta and even iodine–containing medication has resulted in fetal hypothyroidism and large goitres in the newborn.[90,91] With iodides, the goitres are larger and firmer than those produced by antithyroid drugs, defective autoregulation of the fetal and neonatal thyroid gland occurs and escape from the Wolff-Chaikoff effect occurs less readily. In contrast, it was suggested that iodine seldom if ever leads to fetal hypothyroidism. This was based on a study in which a low dose of iodine, only 6 to 40 mg/day, was administered to pregnant women with Graves' disease starting at 11 to 37 weeks gestation. Cord samples at delivery showed 2 of 35 fetuses had a serum free T_4 level above the normal range and none had levels below it. However 22 of the 35 mothers had serum free T_4 levels at delivery slightly above the normal range with 13 within the normal range.[92]

Iodine is avoided as far as possible in the pregnant patient. However, short term use during the second trimester or in treatment of thyrotoxic crisis is unlikely to be detrimental.[93]

5.3 Thyrotoxic Crisis

Thyrotoxic crisis (thyroid storm) is an extremely acute form of hyperthyroidism which tends to occur in patients with Graves' disease rather than toxic nodular disease.[17] Fortunately, thyrotoxic crisis is rare, because it is a life-threatening condition. With respect to pregnancy, this condition is most likely to occur at or after delivery and with toxaemia of pregnancy.[16,94]

Serum T_4 and T_3 levels in the patient with thyrotoxic crisis do not differ from those in the patient with severe uncomplicated hyperthyroidism, but free T_4 and T_3 levels are generally thought to be higher.[17] The diagnosis is made on clinical grounds and treatment should not be delayed while waiting for biochemical results.

Thyrotoxic crisis should be managed in an intensive care unit. This section gives only a brief outline of management of this condition.[17,95]

Dehydration and electrolyte imbalance should immediately be treated with intravenous fluids. β-blockers such as propranolol should be administered. Initially, propranolol 1mg may be administered intravenously over 1 minute and repeated at 2 minute intervals if necessary. The total propranolol dose should not exceed 10mg (5mg if the patient is anaesthetised). Intravenous propranolol should be followed by oral propranolol 40 to 80mg every 6 hours. The relatively cardioselective β-blocker atenolol and the calcium antagonist diltiazem are generally contraindicated in pregnancy, but use of one of these as an alternative to propranolol may have to be considered in patients in thyrotoxic crisis who have bronchial asthma. Usually hydrocortisone 100mg every 6 hours is administered intravenously.

Synthesis of further T_4 and T_3 is prevented by the use of propylthiouracil, initially 600 to 1000mg, followed by 200 to 250mg every 4 hours. Propylthiouracil may be administered as crushed tablets via a nasogastric tube. If there is a history of agranulocytosis or hepatotoxicity, antithyroid drugs should not be used.

After inhibition of thyroid hormone synthesis with propylthiouracil, release of pre-formed thyroid hormone is hindered with iodide, which is administered orally as a saturated solution of potassium iodide 5 drops every 6 hours, or as Lugol's solution 10 drops every 8 hours. A less important effect of this excess iodide is reduction of organification of iodine and consequently of thyroid hormone synthesis.

The cholecystographic agents ipodate 0.5 to 3 g/day and iopanoate 0.5g twice daily are tri-iodoaniline derivatives that inhibit outer ring T_4 deiodinase thereby acutely reducing T_3 levels. As these agents are deiodinated, the inorganic iodide released causes serum T_4 levels to fall.[96] The tri-iodoaniline derivatives may also inhibit binding of thyroid hormone to cell receptors.[97] The rapidity of action of these agents is an advantage in patients with thyrotoxic crisis, but they should probably only be used after delivery.

Other important measures in the management of thyrotoxic crisis are reduction of the patient's temperature, avoidance of aspirin or other salicylates and

maintenance of adequate oxygenation. Cardiac failure and arrhythmias may need conventional treatment, and anticoagulation should be considered in the latter situation.

6. Surgery

Bilateral subtotal thyroidectomy is generally an effective means of treating hyperthyroidism.[41] Because this procedure is performed in the middle trimester, it eliminates the need for antithyroid drugs, which may have effects on fetal growth and function, in the last trimester. Control of hyperthyroidism with antithyroid drugs before surgery is the ideal, but when antithyroid drugs cannot be used a short course of propranolol 20 to 40mg every 8 hours and iodine as Lugol's solution 0.1 to 0.3ml (total iodine 130 mg/ml) every 8 hours should be administered. Postoperatively, propranolol should not be withdrawn abruptly. The dose is halved at 48 hours and the drug is usually discontinued 4 days after surgery. Thyroid hormone replacement in the form of oral T_4 100 μg/day is initiated 2 days after surgery and adjusted according to the serum free T_4 level at 4 weeks after surgery. Thyroid hormone replacement is discontinued within 12 months in most patients.

The risks of surgery to the pregnant woman are not increased beyond those of the nonpregnant patient.[42] With an experienced surgeon, the reported incidence of complications such as postoperative haematoma, recurrent laryngeal nerve palsy and hypoparathyroidism is low (1.2%). The incidence of recurrent hyperthyroidism after bilateral subtotal thyroidectomy has been reported to be 1.4% at 18 months[98] and 1.28% at 5 to 13 years after the procedure.[99]

Hypothyroidism, on the other hand, is common after bilateral subtotal thyroidectomy. After surgery leaving a 3g remnant on each side, hypothyroidism occurs in approximately 50% of patients.[100] However, this is readily treated and for many patients, the scar is the major side effect of surgery.[101] Total thyroidectomy has been advocated by some surgeons for nonpregnant patients with Graves' disease,[102] Graves' disease with severe ophthalmopathy[100] and toxic multinodular goitre,[100] but has not been evaluated in pregnancy.

The older literature shows that the risk of miscarriage and spontaneous labour as a result of bilateral subtotal thyroidectomy is low. In a comparison of medical and surgical treatment, all but 1 of 33 pregnant women with hyperthyroidism who underwent bilateral subtotal thyroidectomy went to term.[43,44] A review of the literature[45] concluded that there was no advantage for one form of treatment over the other; it showed that surgery imposed risks to the pregnancy no greater than those imposed by administration of antithyroid drugs throughout pregnancy. This review compared 318 pregnant women who received antithyroid drugs and 288 who had a thyroidectomy. Of the women who received antithyroid drugs, 80% had a normal delivery and 6%, a premature delivery; the incidence of miscarriage was 10%. The corresponding figures in women who underwent surgery were 91, 1 and 4%, respectively. However, first trimester miscarriages were reported only for those patients who were treated medically. Perinatal infant deaths were 4% with both forms of management.[45] More recently, a report of 20 pregnant women with hyperthyroidism who were treated surgically showed that, with the exception of 1 woman who gave birth at 36 weeks, all went to term. All the infants in this study had normal birth weights, and none had congenital malformations, goitre or thyroid dysfunction.[42]

Bilateral subtotal thyroidectomy, in the prepared patient, performed in the middle trimester by an experienced surgeon with careful anaesthetic supervision avoiding hypotension, hypoxia and drugs known to affect the fetus carries little risk to the mother or fetus and remains a useful option.

7. Hyperthyroidism and Hyperemesis Gravidarum

Nausea and vomiting may occasionally be presenting features of hyperthyroidism, and should be differentiated from hyperemesis gravidarum. The latter is characterised by excessive vomiting in early pregnancy, loss of 3 to 5% of bodyweight, ketonuria and electrolyte disturbance. However, these pa-

tients exhibit few of the other features of hyperthyroidism and do not have detectable thyroid microsomal antibodies. Reduced levels of thyrotropin and elevated T_4 levels have been found in 30 to 60% of patients with hyperemesis but these levels return to normal by 18 weeks of pregnancy.[103,104] This hyperthyroxinaemia is not usually accompanied by clinical signs of hyperthyroidism. However, 2 of 39 patients with hyperemesis gravidarum exhibited such clinical signs in one study.[105]

hCG levels are higher than normal in many but not all pregnant women with hyperemesis. hCG shares a common α subunit with thyrotropin and is believed to stimulate the thyroid via the thyrotropin receptor. Both the severity of vomiting and free T_4 levels have been reported as correlating with hCG levels.[106] However, some uncertainty about the role of hCG was raised when it was found that serum with low levels of hCG, obtained from women who recently had a pregnancy terminated, stimulated thyroid cells to secrete T_4 and T_3 *in vitro*.[107] The explanation appears to be that hCG is a heterogenous protein. Isomers of hCG with low or no sialylation have the greatest thyroid stimulating activity and these are present in high titre in severe vomiting in early pregnancy.[108]

One report described hyperthyroidism in the separate pregnancies of a mother and daughter, each of whom had serum hCG levels which would not normally have been associated with hyperthyroidism.[109] The mechanism was believed to be a mutant thyrotropin receptor which was hypersensitive to hCG.

Supportive measures should be used initially in pregnant women with hyperemesis who exhibit hyperthyroidism. However, if hyperthyroidism persists into the second trimester or is severe, short term antithyroid drug therapy is probably indicated.[53,109]

Hyperthyroxinaemia is not associated with morning sickness.[110]

8. Hyperthyroidism Associated with Trophoblastic Neoplasms

Gestational trophoblastic neoplasms represent a spectrum of pregnancy-related trophoblastic proliferative disorders. They are classified on the basis of clinical features and serum hCG levels rather than histology. The incidence varies from 1 in 1200 to 2000 pregnancies in the US and Western Europe, but is 10 times higher in Eastern Europe and Asia and is more common at the extremes of reproductive age.

From 10 to 50% of patients with trophoblastic disease, which includes either hydatidiform mole or choriocarcinoma, have hyperthyroxinaemia. A much lower proportion are clinically toxic although thyrotoxic crisis has been described.[111] Antithyroid drugs and propranolol are sometimes required but rapid resolution of hyperthyroidism occurs with effective treatment of trophoblastic disease.

9. Postpartum Painless Thyroiditis

A subacute thyroiditis occurs in about 5% of postpartum women.[112-115] It is believed to be caused by a rebound in the immune response after the suppression associated with pregnancy. The condition occurs about 6 to 12 weeks after delivery. Approximately two-thirds of the patients have a hyperthyroid phase which must be differentiated from Graves' disease. Unlike Graves' disease, this condition is attributable to the release of preformed T_4 and T_3 from a damaged thyroid. Symptoms are mild and may easily be missed. This condition is characterised by a high titre of microsomal antibodies, a low technetium or radioactive iodine uptake and absence of TSI. Breastfeeding needs to be discontinued for only 1 day after investigation with technetium.[53] Mild hyperthyroidism may persist for 1 to 2 months in patients with postpartum painless thyroiditis, and is followed in two-thirds of patients by transient hypothyroidism. In one-third of patients the disease will resolve without a hypothyroid phase. A small goitre may occur in half the patients and persist through the hypothyroid phase.[115]

Treatment with a β-blocker should be considered in patients with postpartum painless thyroiditis only if hyperthyroidism is symptomatic. T_4 should be administered if the patient is symptomatically hypothyroid but can usually be discontinued after 6 months. Thyroid function is carefully monitored; most patients return to a euthyroid state within a

year, but about 20% develop permanent hypothyroidism. Annual thyroid function tests should be performed for 5 years in all patients who develop postpartum painless thyroiditis, because these patients are at risk of developing permanent hypothyroidism.[116]

10. Conclusion

In pregnancy, hyperthyroidism is usually caused by Graves' disease. Pregnancy commonly occurs after treatment for hyperthyroidism has been started. Therefore, women of child bearing age should be reminded of the importance of using contraceptive measures when antithyroid drug treatment is started.

Unrecognised or inadequately treated hyperthyroidism has serious effects on the mother and particularly on the pregnancy, the fetus and the neonate. Stillbirths, relative delay in gestational age at diagnosis, preterm delivery and perinatal deaths occur more often than when hyperthyroidism has been diagnosed, and antithyroid drug treatment started before pregnancy. TSI crosses the placenta and infrequently may cause fetal and neonatal hyperthyroidism.

Investigation of hyperthyroidism in pregnancy should include measurement of thyrotropin and free T_4, as total T_4 is raised in normal pregnancy due to increased thyroxine binding globulin levels.

Hyperthyroidism in pregnancy is usually managed throughout with antithyroid drugs, preferably propylthiouracil. Antithyroid drugs readily cross the placenta but the latter is a significant barrier to the passage of thyrotropin, T_4 and T_3. As the fetal thyroid is fully responsive to antithyroid drugs (and TSI) by 20 weeks gestation, the smallest dose which will control maternal hyperthyroidism is used.

There is little evidence to suggest that fetal malformation occurs more commonly than normal in hyperthyroidism whether treated with antithyroid drugs or not. Fetal and neonatal hypothyroidism, however, is a possible outcome of antithyroid drug management of the mother. A block and replacement regimen should not be used. This exposes the fetus to high doses of antithyroid drug and to the risk of hypothyroidism; thyroxine given to the mother does not cross the placenta in sufficient quantity to avoid this risk. Maternal serum free T_4 is the most practical index of fetal thyroid function and the dose of antithyroid drug should aim to keep this in the high normal range. Intellectual and physical development of children born to mothers treated with antithyroid drugs is unimpaired.

Failure to control hyperthyroidism on a 'small' dose of antithyroid drug or adverse reactions to them are now the most common indications for bilateral subtotal thyroidectomy in pregnancy. Surgery is performed during the middle trimester ideally on a patient prepared with antithyroid drugs but otherwise after a short course of propranolol and iodine. Surgery is an effective form of treatment and removes concern about the effects of hyperthyroidism or antithyroid drugs on fetal growth and function.

Transient depression of thyrotropin and an elevated thyroxine, but rarely clinical hyperthyroidism, occurs in some patients with hyperemesis gravidarum. This is related to the thyroid stimulating effect of hCG in early pregnancy. Similarly hyperthyroxinaemia and even overt hyperthyroidism occur with trophoblastic neoplasms. Hyperthyroidism in post partum painless thyroiditis is due to the release of preformed thyroid hormone from a damaged thyroid. These conditions should be distinguished from Graves' disease. At a suitable time after the pregnancy definitive treatment of Graves' disease should be offered.

References

1. Davis LE, Lucas MJ, Hankins GD, et al Thyrotoxicosis complicating pregnancy. Am J Obstet Gynecol 1989; 160: 63-70
2. Lim BH, Raman S, Sivanesaranam V, et al. Thyrotoxicosis in pregnancy: a six year review. Singapore Med J 1989; 30: 539-41
3. Burrow GN. Thyroid function and hyperfunction during gestation Endocrine Rev 1993; 14: 194-202
4. Hamburger JI. Diagnosis and management of Graves' disease in pregnancy. Thyroid 1992; 2: 219-24
5. Vanderpump MPJ, Tunbridge WMG, French JM, et al. The incidence of thyroid disorders in the community: a twenty year follow up of the Whickam study. Clin Endocrinol 1995; 43: 55-68
6. Becks GP, Burrow GN. Thyroid disease and pregnancy. Med Clin North Am 1991; 75: 121-50
7. Reed Larsen P, Ingbar SH. The thyroid gland. In: Wilson JD, Foster DW, editors. Williams' textbook of endocrinology. 8th ed. Philadelphia: WB Saunders, 1992; 357-487

8. ACOG Technical Bulletin No 181. Thyroid disease in pregnancy. Int J Gynecol Obstet 1993; 43: 82-8
9. Farwell AP, Braverman LE. Thyroid and antithyroid drugs. In: Hardman JG, Limbird LE, Molinoff PB, et al., editors. Goodman & Gilman. The pharmacological basis of therapeutics. 9th ed. McGraw Hill, 1995: 1383-409
10. Glinoer D, De Nayer P, Bordoux P, et al Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990; 71: 276-97
11. Harada K, Hirshman JM, Reed AW, et al. Comparison of thyroid stimulators and thyroid hormone concentrations in sera of pregnant women. J Clin Endocrinol Metab 1979; 48: 793-7
12. Ain KB, Refetoff S. Relationship of oligosaccharide modification to the cause of serum thyroxine-binding globulin excess. J Clin Med Endocrinol Metab 1988; 66: 1037-43
13. Surks MI, Chopra IJ, Mariash CN, et al. American thyroid association guidelines for use of laboratory tests in thyroid disorders. JAMA 1990; 263: 1529-32
14. Momotani N, Ito K, Hamada N, et al. Maternal hyperthyroidism and congenital malformation in the offspring. Clin Endocrinol 1984; 20: 695-700
15. Ross McDougall. I Hyperthyroidism & maternal - fetal thyroid hormone metabolism. In: Brody SA, Ueland K, editors. Endocrine disorders in pregnancy. Connecticut: Appleton & Lange, 1989; 151-63
16. Menon V, McDougall WW, Leatherdale BA. Thyrotoxic crisis following eclampsia and induction of labour. Postgrad Med J 1982; 58: 286-7
17. Tietgens ST, Leinung MC. Thyroid storm. Med Clin North Am 1995; 79: 169-84
18. Bruner JP, Landon MB, Gabbe SG. Diabetes mellitus and Graves' disease complicated by maternal allergies to antithyroid drugs. Obstet Gynecol 1988; 72: 443-5
19. Lazarus JH, Othman S. Thyroid disease in relation to pregnancy. Clin Endocrinol 1991; 34: 91-3
20. Montoro M, Mestman JH. Graves' disease and pregnancy. N Engl J Med 1981; 305: 48
21. Thorpe-Beeston JF, Nicolaides KH, Felton CV, et al Maturation of the secretion of thyroid hormone and thyroid stimulating hormone in the fetus. N Engl J Med 1991; 324: 532-6
22. Fisher DA. Thyroid function in very low birth weight infants Clin Endocrinol 1997; 47: 419-21
23. Roti E, Gnudi A, Braverman LE. The placental transport synthesis and metabolism of hormones and drugs which affect thyroid function. Endocrinol Rev 1983; 4: 131-49
24. Vulsma T, Gons MH, De Vijlder JM. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect of thyroid agenesis. N Engl J Med 1989; 321: 13-6
25. Munro DS, Dirmikis SM, Humphries H, et al. The role of thyroid stimulating immunoglobulins of Graves' disease in neonatal thyrotoxicosis. Br J Obstet Gynecol 1978; 85: 837-43
26. Khoury MJ, Becerra JE, D'Almida PJ. Maternal thyroid disease and risk of birth defects in offspring: a population based control study. Paediatr Perinat Epidemiol 1989; 3: 402-20
27. Wing DRA, Millar LK, Koonings PP, et al. A comparison of propylthiouracil versus methimazole in the treatment of hyperthyroidism in pregnancy. Am J Obstet Gynecol 1994; 170: 90-5
28. Cooper DS. Antithyroid drugs. N Engl J Med 1984; 311: 1353- 62
29. Marchant B, Brownlie BEW, Hart DM, et al. The placental transfer of propylthiouracil, methimazole and carbimazole. J Clin Endocrinol Metab 1977; 45; 1187-92
30. Senior B, Chernoff HL. Iodide goiter in the newborn. Pediatrics 1971; 47: 510-5
31. Salvi M, How J. Pregnancy and autoimmune thyroid disease. Endocrinol Metab Clin North Am 1987; 16: 431-44
32. Amino N, Kuro R, Tanizawa O, et al. Changes of serum antithyroid antibodies during and after pregnancy in autoimmune thyroid disease. Clin Exp Immunol 1978; 31: 30-7
33. Wartofsky L, Glinoer D, Spolomon B, et al. Differences and similarities in the diagnosis and treatment of Graves' disease in Europe, Japan and the United States. Thyroid 1991; 1: 129-35
34. Franklyn JA, Daykin J, Drole Z, et al. Long term follow up of treatment of thyrotoxicosis by three different methods. Clin Endocrinol (Oxf) 1991; 34: 71-6
35. Sheldon J, Reid DJ. Thyrotoxicosis: changing trends in treatment. Ann R Coll Surg Engl 1986; 68: 283-5
36. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995; 273: 808-12
37. Lazarus JH. Guidelines for the use of radioactive iodine in the management of hyperthyroidism. J R Coll Phys Lond 1995; 29: 464-9
38. O'Doherty MJ, McElhatton PR, Thomas SHI. Treating thyrotoxicosis in pregnant or potentially pregnant women. BMJ 1999; 1: 5
39. Patwardhan NA, Moroni M, Rao S, et al. Surgery still has a role in Graves' hyperthyroidism. Surgery 1993; 114: 1108-13
40. Belchetz PE. Thyroid disease in pregnancy. BMJ 1987; 294: 264-5
41. Stice RC, Grant CS, Gharib H, et al The management of Graves' disease during pregnancy. Surg Gynecol Obstet 1984; 158; 157-60
42. Ghaneim A, Atkins P. Management of thyrotoxicosis in pregnancy. Int J Clin Pract 1998; 52: 36-8
43. Hawe P, Francis HH. Pregnancy and thyrotoxicosis. BMJ 1962; 2: 817-22
44. Hawe P. The management of thyrotoxicosis during pregnancy. Br J Surg 1965; 52: 731-4
45. Pekonen F, Lamberg BA. Thyrotoxicosis during pregnancy Ann Chir Gynaecol 1978; 67: 165-73
46. Astwood EB. Treatment of hyperthyroidism with thiourea and thiouracil. JAMA 1943; 122: 78-81
47. Franklyn JA. The management of hyperthyroidism. N Engl J Med 1994; 330: 1731-8
48. Carbimazole. Therapeutic drugs. Vol 1. Dollery C, editor. Edinburgh: Churchill Livingstone, 1991; C66-69
49. Propylthiouracil therapeutic drugs. Vol 2. Dollery C, editor. Edinburgh: Churchill Livingstone, 1991: P282-287
50. Totterman TH, Karlsson FA, Bengtsson M. Induction of circulating activated suppressor-like T cells by methimazole therapy for Graves' disease. N Engl J Med 1987; 316: 15-22
51. Cooper DS. Which anti-thyroid drug? Am J Med 1986; 80: 1165-8
52. Cooper DS, Goldminz D, Levin AA, et al. Agranulocytosis associated with antithyroid drugs: effects of patient age and drug dose. Ann Intern Med 1983; 98: 26-9
53. Vanderpump MPJ, Ahlquist JAO, Franklyn JA, et al. Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. BMJ 1996; 313: 539-44
54. Meyer-GeBner M, Benker G, Lederbogen S. Antithyroid drug induced agranulocytosis. Clinical experience with ten patients treated at one institution and review of the literature. J Endocrinol Invest 1994; 17: 29-36
55. Mujitaba Q, Burrow GN. Treatment of hyperthyroidism in pregnancy with propylthiouracil and methimazole. Obstet Gynecol 1975; 46: 282-6

56. Milham Jr S, Elledge W. Maternal methimazole and congenital defects in children. Teratology 1972; 5: 125-6
57. Van Dijke CP, Heydendael RJ, De Kleine MJ. Methimazole, carbimazole, and congenital skin defects. Ann Intern Med 1987; 106: 60-1
58. Cheron RG, Kaplan MM, Larsen PR, et al. Neonatal thyroid function after propylthiouracil therapy for maternal Grave' disease. N Engl J Med 1981; 304: 525-8
59. Momotani N, Noh J, Oyanagi H, et al. Antithyroid drug therapy for Grave's disease during pregnancy. N Engl J Med 1986; 315: 24-8
60. Burrow GN, Bartsosocas C, Klatskin EH, et al. Children exposed in utero to propylthiouracil: subsequent intellectual and physical development. Am J Dis Child 1968: 116; 161-5
61. McCarroll AM, Hutchinson M, McAuley R, et al. Long term assessment of children exposed in utero to carbimazole. Arch Dis Child 1976; 51: 532-6
62. Messer PM, Hauffa BP, Olbricht T, et al. Antithyroid drug treatment of Graves' disease in pregnancy: long term effects on somatic growth, intellectual development and thyroid function in offspring. Acta Endocrinol (Copenh) 1990; 123: 311-6
63. Mandel SJ, Brent Ga, Larsen PR. Review of antithyroid drug use in pregnancy and report of a case of aplasia cutis. Thyroid 1994; 4: 129-33
64. Kampmann JP, Johansen K, Hansen JM, et al. Propylthiouracil in human milk: revision of dogma. Lancet 1980; I: 736-7
65. Mortimer RH, Cannell GR, Addison RS, et al. Methimazole and propylthiouracil equally cross the perfused human term placenta lobule. J Clin Endocrinol Metab 1997; 82; 3099-102
66. Benker G, Vitti P, Kahal G, et al. Response to methimazole in Graves' disease. Clin Endocrinol 1995; 43: 259-63
67. Okamura K, Ikenoue H, Shiroozu A, et al. Reevaluation of the effects of methylmercaptoimidazole and propylthiouracil in patients with Graves' hyperthyroidism. J Clin Endocrinol Metab 1987; 65: 719-23
68. Romaldini JH, Bromberg N, Werner RS, et al. Comparison of effects of high and low dose regimens of antithyroid drugs in the management of Graves; hyperthyroidism. J Clin Endocrinol Metab 1983; 57: 563-70
69. Jorde R, Yire-Arne K, Stormer J, et al. Short term treatment of Graves' disease with methimazole in high versus low doses. J Intern Med 1995; 238: 161-5
70. Meng W, Meng S, Manchen E, et al. Effect of therapy duration and low and highly dosed thiamazole treatment on Basedow Graves' disease. Exp Clin Endocrinol 1991; 97: 257-60
71. Reinwen D, Benker JH, Lazarus JH, et al. A prospective randomized trial of antithyroid drug in Graves' disease therapy. European Multicentric Study Group on Antithyroid drug treatment. J Clin Endocrinol Metab 1993; 76: 1516-21
72. Wilson R, Buchanan L, Fraser WD, et al. Do higher doses of carbimazole improve remission in Graves' disease? Q J Med 1996; 89: 381-5
73. Hashizume K, Ichikawa K, Sakurai A. Administration of thyroxine in treated Graves' disease: effects on the level of antibodies to thyroid stimulating receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med 1991; 324: 947-53
74. Edmonds CJ, Telez M. Treatment of Graves' disease by carbimazole high dose with thyroxine compared to titration dose. Eur J Endocrinol 1994; 131: 120-4
75. McIver B, Rae P, Beckett G, et al. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an antithyroid drug. N Engl J Med 1996; 334: 220-4
76. Allanic R, Fauchet J, Orgiazzi AM, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990; 70: 675-9
77. Weetman AP, Pickerell AP, Watson P. Treatment of Graves' disease with the block-replace regimen of antithyroid drugs: the effect of treatment duration and immunogenetic susceptibility on relapse. Q J Med 1994; 87: 337-41
78. Hashizume K, Ichikawa K, Nishi Y, et al. Effect of administration of thyroxine on the risk of post partum recurrence of hyperthyroid Graves' disease. J Clin Endocrinol Metab 1992; 75: 6-10
79. Ramsay I, Kaui S, Krassas G. Thyrotoxicosis in pregnancy: results of treatment by antithyroid drugs combined with T_4. Clin Endocrinol 1983 18: 73-85
80. Kriplani A, Buckshee K, Bhargava VL, et al. Maternal and perinatal outcome in thyrotoxicosis complicating pregnancy. Eur J Obstet Gynecol Reprod Biol 1994; 54: 159-63
81. Girling JA. Thyroid disease and pregnancy. Br J Hosp Med 1996; 56: 316-20
82. Matsuura N, Fujieda K, Yasuhiro I, et al. thyrotropin receptor antibodies in mothers with Graves' disease and outcome in their offspring. Lancet 1988; I: 14-8
83. Ogilvy-Smith AL. Endocrinology of the neonate. Br J Hosp Med 1995; 54: 207-11
84. Rubin PC. Beta Blockers in pregnancy. N Engl J Med 1981; 305: 1323-6
85. Bullock JL, Harris RE, Young R. Treatment of thyrotoxicosis during pregnancy with propranolol. Am J Obstet Gynecol 1973; 121: 242-5
86. Gladstone GR, Hordof A, Gersony WM. Propranolol administration during pregnancy: effects on the fetus. J Pediatr 1975; 86: 962-4
87. Ueland K, McAnulty JH, Ueland FR, et al. Special consideration in the use of cardiovascular drugs. Clin Obstet Gynecol 1981; 24: 809-23
88. Propranolol therapeutic drugs. Vol 1. Dollery C, editor. Edinburgh,: Churchill Livingstone, 1991; 272-8
89. Campbell JW. A possible teratogenic effect of propranolol [letter]. N Engl J Med 1985; 313: 518
90. Kyle PM, Redman CW. Comparative risk-benefit assessment of drugs used in the management of hypertension in pregnancy. Drug Saf 1992; 7: 223-34
91. Carswell F, Kerr MM, Hutchison JH. Congenital goiter and hypothyroidism produced by maternal ingestion of iodides. Lancet 1970; I: 1241-3
92. Momotani N, Hisaoka T, Noh J, et al. Effects of iodine on thyroid status of fetus versus mother in treatment of Grave's disease complicated by pregnancy. J Clin Endocrinol Metab 1992; 75: 738-44
93. Iodine therapeutic drugs. Vol 1. Dollery C, editor. Edinburgh: Churchill Livingstone, 1991: I146-8
94. Kamm ML, Weaver JC, Page EP, et al. Acute thyroid storm precipitated by labour. Obstet Gynecol 1963; 21; 460-3
95. Burch HB, Wartofsky L. Life threatening thyrotoxicosis: thyroid storm. Endocrinol Metab Clin North Am 1993; 22: 263-77
96. Cooper D. Treatment of thyrotoxicosis. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's The thyroid. 6th ed. Philadelphia (PA): Lippincott, 1991: 887-916
97. Wartofsky L. Thyroid storm. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's The thyroid. 6th ed. Philadelphia (PA): Lippincott, 1991: 871-9
98. Reid DJ, Hyperthyroidism and hypothyroidism complicating the treatment of thyrotoxicosis. Br J Surg 1987; 74: 1060-2
99. Davenport M, Talbot JN, Thyroidectomy for Graves' disease: is hypothyroidism inevitable? Ann R Coll Surg Engl 1989; 71: 87-91

100. Younes N, Robinson B, Delbridge L. The aetiology, investigation and management of surgical disorders of the thyroid gland. Aust NZ J Surg 1996; 66: 481-90
101. Ross McDougall I Graves' disease: current concepts. Med Clin North Am 1991; 75: 79-95
102. Miccoli P, Vitti P, Rago T, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery 1996; 120: 1020-5
103. Swaminathan R, Chin RK, Lao TTH, et al. Thyroid function in hyperemesis gravidarum. Acta Endocrinol 1989; 120: 155-60
104. Goodwin TM, Montoro M, Mestman J. Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. Am J Obstet Gynecol 1992; 167: 648-52
105. Lao TT, Chin RKH, Chung AMZ. The outcome of hyperemetic pregnancies complicated by transient hyperthyroidism. Aust NZ J Obstet Gynecol 1987; 27: 99-101
106. Goodwin TM, Montoro M, Mestman JH, et al. The role of chorionic gonadotrophin in transient hyperthyroidism of hyperemesis gravidarum. J Clin Endocrinol Metab 1992 75 1333-7
107. Kennedy RL, Darne J, Cohen M, et al. Human chorionic gonadotropin (hCG) may not be responsible for the thyroid stimulating activity in normal pregnancy serum. J Clin Endocrinol Metab 1991; 72: 258-63
108. Tsurata E, Tada H, Tamaki H, et al. Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. J Clin Endocrinol Metab 1995; 80: 350-5
109. Rodien P, Bremont C, Raffin Sanson ML, et al. Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. N Engl J Med 1998; 339: 1823-6
110. Evans AJ, Li TC, Selby C, et al. Morning sickness and thyroid function. Br J Obstet Gynaecol 1986; 93: 520-2
111. Rajatanavin R, Chailurkit LO, Srisupandit S, et al. Trophoblastic hyperthyroidism. Clinical and biochemical features of five cases. Am J Med 1988; 85: 237-41
112. Amino N, Mori H, Iwatani Y, et al. High prevalence of transient post-partum thyrotoxicosis and hypothyroidism. N Engl J Med 1982; 306: 849-52
113. Nikolai TF, Turney SL, Roberts RC. Post partum lymphocytic thyroiditis: prevalence: clinical course and long term follow up. Arch Intern Med 1987; 147: 221-4
114. Walfish PCG, Meyerson J, Provias JP, et al. Prevalence and characteristics of post-partum thyroid dysfunction: results of a survey from Toronto, Canada. J Endocrinol Invest 1992; 15: 265-72
115. Roti E, Emerson CH. Postpartum thyroiditis. J Clin Endocrinol Metab 1992; 74: 3-5
116. Othman S, Philips DIW, Parkes AB, et al. A long term follow up of postpartum thyroiditis. Clin Endocrinol 1990; 32: 559-64

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