The management of thyroid disease in pregnancy

O. M. EDWARDS
M.D., M.R.C.P.

Addenbrooke's Hospital, Hills Road, Cambridge

Summary

The management of hyperthyroidism and hypothyroidism in pregnancy is discussed and illustrated with appropriate cases. The dangers of the usage of high doses of antithyroid drugs and of propranolol are described.

Introduction

The profound changes induced by pregnancy on the metabolism of iodine and the formation and transport of thyroidal hormones have been described (Feely, 1979). In consequence certain facts should be borne in mind when faced with the diagnosis and management of thyroid disease in pregnancy; firstly, the increase in thyroidal binding proteins vitiates the standard thyroid function tests whilst radio-iodine uptake tests are avoided; secondly, the placental transfer of thyroid hormones is uncertain (Werner, 1967); thirdly, the easy passage of antithyroid drugs to the fetus modifies the therapeutic approach (Burrow, 1978).

The increased incidence of goitre in pregnancy is linked with altered physiological demands and has been dealt with in a previous paper (Feely, 1979) so the discussion will be limited to the diagnosis and management of thyrotoxicosis and treated hypothyroidism.

Graves' disease is a relatively common disorder in reproductive years and its coincidence with pregnancy occurs from time to time in the thyroid clinic. Usually the disease is mild and its management poses little difficulty, but the neglected patient may present with thyrotoxic heart failure or very rarely, at parturition, with thyroid storm.

The main problems are the diagnosis of mild thyrotoxicosis in pregnancy, the alternatives of medical or surgical management, the modifications of antithyroid drug regimes since the physical and intellectual development of the offspring may be impaired by the exhibition of antithyroid drugs in pregnancy and, finally, the place of β -adrenergic blocking drugs.

Pregnancy with its increased metabolic rate, increased incidence of goitre, lid lag and rise in the serum thyroxine and triiodothyronine mimics Graves' disease. The distinction is difficult on clinical

grounds particularly when faced with an anxious woman in advanced pregnancy with lid lag, heat intolerance, a small goitre, warm hands, and a sinus tachycardia. Since the absolute levels of thyroxine and triiodothyronine cannot be taken as diagnostic and radio-iodine tests are contra-indicated, a test which estimates the circulating free thyroxine level – a level which remains constant in pregnancy despite alterations in the binding globulins should be used. As discussed in the previous paper (Feely, 1979), the thyroxine index is derived from the T_4 resin uptake and the serum thyroxine measured by radioimmunoassay and thus relates to the levels of free hormone. If the free thyroxine index is raised, then the diagnosis is confirmed. If the test is equivocal and clinical suspicion is strong, then an absent thyrotrophin (TSH) response to thyroliberin will confirm the diagnosis.

When the diagnosis has been made and confirmed, the choice of treatment remains. Radio-iodine is absolutely contra-indicated because of its possible effects on the fetus and the genetic mutation rate. Partial thyroidectomy in pregnancy does not carry an increased risk of miscarriage. The standard teaching in the U.K. is to perform the operation only in the latter half of the second trimester, although many advocates of this treatment in the U.S.A. will perform the operation in the first and second trimester without apparent ill effects to the fetus or mother, avoiding postoperative maternal hypothyroidism by giving replacement thyroxine routinely (Burrow, 1978). However, the present author has yet to see a partial thyroidectomy performed in pregnancy or seen any indication for it.

The treatment of choice is therefore drug therapy using either propylthiouracil or carbimazole. Both drugs block the organification of iodine but propylthiouracil has the theoretical advantage of partially blocking the peripheral de-iodination of thyroxine to triiodothyronine (Slingerland and Burrows, 1962).

There is a further choice, namely to give the antithyroid drugs in slightly higher dosages together with thyroidal hormones to avoid maternal and fetal hypothyroidism, or to use the smallest dose of carbimazole capable of maintaining euthyroidism.

The policy of using antithyroid drugs together

with thyroxine or triiodothyronine may be criticized on several counts. The transport of thyroxine and triiodothyronine across the placenta is slow and uncertain, whilst antithyroid drugs easily cross the placenta. Thus, if the policy of virtually complete blockade of maternal thyroidal hormone production with maintenance of maternal euthyroidism by oral triiodothyronine or thyroxine is adopted, then the fetal thyroid will be exposed to high levels of antithyroid drugs whilst insufficient thyroidal hormones will cross the placental barrier to maintain fetal euthyroidism. The development of goitres in infants born to patients taking antithyroid drugs probably results from increased secretion of fetal TSH in response to depressed fetal hormone production induced by placental transport of these drugs. The concurrent administration of triiodothyronine does not prevent high fetal thyrotropin levels and presumed intra-uterine fetal hypothyroidism (Low, Ratcliffe and Alexander, 1978). However, the goitre that may occur in the thioamide-treated woman is rarely large and obstructing, as used to occur in iodide-induced goitre, and whilst cretinism has been reported in treated women there is no evidence that it was caused by the drugs.

The safest policy is illustrated in Fig. 1. At the time of diagnosis the patient was clinically thyrotoxic and the diagnosis was confirmed by finding a raised free thyroxine index. Treatment was started with

carbimazole 10 mg 8-hourly, the patient being warned to report any untoward symptoms. Within one month the disorder was well controlled and treatment was adjusted throughout pregnancy by the patient's clinical response, attempting to keep the free thyroxine index in the high normal range with the lowest possible dose of the drug. The patient was delivered of a healthy euthyroid infant with a bone age compatible with gestation.

In conclusion, one should attempt to keep the free thyroxine index in the upper end of the normal range with the lowest possible dose of carbimazole. If one suspects hypothyroidism at any stage, thyroxine should be added in the usual dosage. The drugs should be stopped if possible in the last trimester.

There are a few special problems which may occur in the untreated and neglected patient who presents in late pregnancy.

Case report

A 25-year-old woman presented in late pregnancy in severe congestive cardiac failure with a marked tachycardia, bounding pulse, fine tremor and a large goitre with a bruit. She gave a history of increasingly severe heat intolerance, palpitations, irritability, ankle swelling and breathlessness.

As she was in marked high output cardiac failure she was given large doses of frusemide, and was digitalized. The thyrotoxicosis was treated with

FIG. 1. The response of serum T_4 and free thyroxine index to treatment with carbimazole in pregnancy.

Lugol's iodine to block thyroxine release and iodine uptake, and propylthiouracil to block the organification of iodine and decrease the peripheral conversion of thyroxine to triiodothyronine.

Despite intensive treatment she remained in heart failure until a day later she delivered a dead fetus. Following delivery she had a massive diuresis and her heart failure rapidly improved. Subsequently she had a partial thyroidectomy.

Following delivery the drug regime may require to be modified but it should be remembered that both carbimazole and propylthiouracil are secreted in breast milk and if high doses are required then the patient should be advised to discontinue breast-feeding.

A rare but interesting complication may occur which is of interest to neonatologists – that is the development of neonatal thyrotoxicosis. Thyroid-stimulating immunoglobulin crosses the placental barrier and in rare cases where titres are high causes neonatal Graves' disease. The disease is self-limiting, lasts about 6 weeks and is treated with propranolol and carbimazole in the usual way. A noteworthy point is that the affected infant may be born to a euthyroid mother who has had treatment in the past.

Do children exposed to antithyroid drugs *in utero* develop normally both physically and intellectually? Burrow *et al.* (1968) compared 18 children exposed to propylthiouracil *in utero* with 18 non-exposed siblings and found no difference in their physical and mental characteristics.

Propranolol and certain other β blockers have become a useful adjunct to the initial treatment of the thyrotoxic patient since many of the manifestations of Graves' disease are mediated *via* the sympathetic nervous system (Bayliss and Edwards, 1971). The exhibition of a β -blocker may ameliorate many of the symptoms but not the increased metabolic rate.

Since the disorder in many patients is very mild, propranolol was suggested as an alternative drug for the treatment of thyrotoxicosis in pregnancy. However, the use of β -receptor blocking drugs poses problems in pregnancy. In one study, the offspring of women who had received propranolol during pregnancy were significantly more depressed than those who had received placebos (Tunstall, 1969).

In another study the use of propranolol was associated with small placenta, intra-uterine growth

retardation, bradycardia and hypoglycaemia (Gladstone, Hardof and Gersony, 1975). It has therefore been felt that propranolol should not be used as the primary agent in the long-term treatment of thyrotoxicosis in pregnancy.

Patients with hypothyroidism rarely become pregnant although pregnancy when it occurs proceeds normally and there is no marked effect on the fetus. However, the treatment of patients with established hypothyroidism on replacement therapy does occur from time to time. The author's policy is to keep the free thyroxine index in the upper range increasing the thyroxine replacement dosage from the usual 0.15–0.2 mg to 0.3 mg if necessary. One must of course remember that the infant born to such a mother may develop neonatal thyrotoxicosis if the original condition had been Graves' disease which had subsequently been treated with, say, partial thyroidectomy.

In conclusion, the commonest thyroid condition requiring treatment in pregnancy is thyrotoxicosis and this should be of little problem provided the smallest possible dosage of antithyroid drugs is used with adequate biochemical monitoring.

References

- BAYLISS, R.I.S. & EDWARDS, O.M. (1971) Urinary excretion of free catecholamines in Graves' disease. *Journal of Endocrinology*, **49**, 167.
- BURROW, G.N. (1978) Hyperthyroidism during pregnancy. *New England Journal of Medicine*, **298**, 150.
- BURROW, G.N., BARTSOCAS, C., KLATSKIN, E.H. & GRUNT, J.A. (1968) Children exposed *in utero* to propylthiouracil. Subsequent intellectual and physical development. *American Journal of Diseases of Children*, **116**, 161.
- FEELY, J. (1979) The physiology of thyroid function in pregnancy. *Postgraduate Medical Journal*, **55**, 336.
- GLADSTONE, G.R., HARDOF, A. & GERSONY, W.M. (1975) Propranolol administration during pregnancy: effects on the fetus. *Journal of Pediatrics*, **86**, 962.
- LOW, L.C.K., RATCLIFFE, W.A. & ALEXANDER, W.D. (1978) Intrauterine hypothyroidism due to antithyroid drug therapy for thyrotoxicosis during pregnancy (Letter). *Lancet*, **i**, 370.
- SLINGERLAND, D.W. & BURROWS, B.A. (1962) Inhibition by propylthiouracil of the peripheral metabolism of radiothyroxine. *Journal of Clinical Endocrinology and Metabolism*, **22**, 511.
- TUNSTALL, M.E. (1969) The effect of propranolol on the onset of breathing at birth. *British Journal of Anaesthetics*, **41**, 792.
- WERNER, S.C. (1967) Hyperthyroidism in the pregnant woman and neonate. *Journal of Clinical Endocrinology and Metabolism*, **27**, 1637.