REVIEW ARTICLES

Management of endocrine disorders in pregnancy Part I*—thyroid and parathyroid disease

Z. M. VAN DER SPUY
M.B.Ch.B., M.R.C.O.G.

H. S. JACOBS
M.D., F.R.C.P.

Cobbold Laboratories, Thorn Institute, Middlesex Hospital Medical School, London W1

In these reviews we discuss the management of endocrine disorders, with the exception of diabetes mellitus, as they occur in pregnancy. Although taking account of the literature, so far as it is possible we give our own opinions as to optimal management and, where appropriate, provide illustrative case reports. Part I deals with disorders of the thyroid and parathyroid glands, Part II with disorders of the pituitary, adrenals and ovaries.

Thyroid

While the basal metabolic rate increases in pregnancy by 20-25%, when it is corrected for the fetal contribution it falls within the normal range and the pregnant woman should be regarded as euthyroid (Burrow, 1978). During pregnancy the thyroid gland enlarges because of hyperplasia of the follicular epithelium, an increase in the size and number of follicles and an increase in the vascularity of the gland (Komins, Snyder and Schwarz, 1975). Because pregnancy goitre occurs commonly in areas with a low iodine intake, one possible stimulus is relative iodine deficiency. Alterations in the handling of iodine in pregnancy also contribute and are caused, firstly by an increase in the glomerular filtration rate (which increases renal losses of iodide) and secondly, because fetal demands on the maternal iodide pool, which are mediated through active placental transport mechanisms, are met preferentially and may therefore result in maternal iodine deficiency (Ingbar and Woeber, 1981). The concentration of thyroxine-binding globulin doubles in the first trimester because its production by the liver is stimulated by the high levels of oestrogen found in pregnancy. As a result serum concentrations of total thyroxine (T_4) and tri-iodothyronine (T_3) and reverse T_3 rise. There

is less certainty about the concentrations of the free (unbound) thyroid hormones, some workers reporting an increase (Yamamoto *et al.*, 1979) and others a fall of free thyroxine concentrations (Smith and Bold, 1983). Analysis of the methodological problems supports the more recent observations that pregnancy is, in fact, associated with a small reduction in maternal plasma free thyroxine concentration (Ekins, 1979).

For the clinician, the most useful index of maternal thyroid function during pregnancy is an accurately measured serum free thyroxine concentration although for the practical management of pregnant patients with thyroid disease, the free thyroxine index is satisfactory. This index can be calculated by relating the product of the total thyroxine concentration and the $^{125}\text{I-T}_3$ resin uptake (an estimate of available thyroxine binding sites in serum) of the patient with that of the normal population. The normal range of thyroid function tests during pregnancy is shown in Table 1.

Hypothyroidism

Untreated hypothyroidism during pregnancy is extremely rare and only 47 cases have been identified in the world literature since 1897 (Montoro *et al.*, 1981). The reports suggest that maternal hypothyroidism has few adverse effects on the fetus since fetal thyroid function is autonomous and, with the exception of its iodine supply, is independent of the mother (Fisher, 1975; Fisher and Klein, 1981). There may however be a risk to the fetus if severe maternal hypothyroidism is present prior to development of the fetal thyroid gland (Pharoah *et al.*, 1981).

Most patients with hypothyroidism who have entered pregnancy are already on treatment. The dose of thyroxine for pregnant women does not need to be changed and is therefore normally 150-200 μg

*Part II of this review will be published in *Postgraduate Medical Journal*, May 1984 issue.

TABLE 1. Mean thyroid hormone levels (± 2 s.d.) at different stages in pregnancy (Smith and Bold, 1983)

Thyroid hormone	Trimester		
	First (n = 56)	Second (n = 70)	Third (n = 80)
Thyroxine (T_4) (nmol/l)	104 $\pm$ 20	135 $\pm$ 30†	144 $\pm$ 34†
Thyroxine binding globulin (TBG) (mg/l)	14.8 $\pm$ 4.2	23.1 $\pm$ 9.8†	32.5 $\pm$ 5.1†
T_4 /TBG ratio	8.7 $\pm$ 2.2	5.3 $\pm$ 3.1†	4.1 $\pm$ 2.0†
Free thyroxine (pmol/l)	15.2 $\pm$ 3.4	13.8 $\pm$ 4.0	10.2 $\pm$ 3.7†
T_3 (nmol/l)	2.6 $\pm$ 0.6	3.4 $\pm$ 0.8†	3.4 $\pm$ 0.9†
TSH (miu/l)	4.9 $\pm$ 2.2	5.8 $\pm$ 1.1*	4.8 $\pm$ 1.3

Significance of difference compared with first trimester. * $P < 0.05$; † $P < 0.001$.

of L-thyroxine per day. It seems reasonable to check thyroid function tests at booking and again at the post-natal visit. Only if these tests are abnormal or if the patient develops signs of hypothyroidism during pregnancy, is more detailed investigation required. The cause of most cases of hypothyroidism is autoimmune thyroiditis. A few patients will have had Graves' disease treated by partial thyroidectomy or ^{131}I and babies of these patients are definitely at risk (see later). A very few will be suffering from hypothyroidism secondary to pituitary disease (see Part II of this review).

No special arrangements are necessary for labour, lactation or contraception. The combined birth-control pill is not contra-indicated in cases of treated hypothyroidism.

Cretinism

There are two forms of cretinism. Sporadic cretinism refers to neonatal hypothyroidism and is usually caused by intrinsic defects of thyroid hormone synthesis, absence of the thyroid, inadvertent iodine or radioiodine treatment of pregnant women and, perhaps most importantly, over-treatment of pregnant thyrotoxic women with anti-thyroid medication (see below). Hypothyroidism of the newborn is essentially a remediable condition which occurs spontaneously in about 1 in 4,000 deliveries and should be routinely detected by neonatal thyroid screening programmes (Klein, 1979). Early diagnosis and treatment is of paramount importance since the prognosis is so closely related to the age of initiation of treatment (Hulse *et al.*, 1982).

Endemic cretinism occurs in areas of the world that are deficient in iodine; the parents are usually goitrous. The condition involves a specific neurological disturbance, although the patient may also be hypothyroid. Treatment with thyroxine reverses the hypothyroidism but the neurological defect (which often causes deaf mutism and spasticity) does not recover. Its cause is unknown but it may be related to

iodine deficiency in the developing brain (Editorial, 1972).

Hyperthyroidism

The prevalence of hyperthyroidism in pregnancy is about 2/1,000 (Ramsay, 1980). The most common cause is Graves' disease, which in non-iodine deficient areas of the world is responsible for 95% of the cases seen during pregnancy. Other causes include toxic multinodular goitre and a single active nodule. In trophoblastic disease, large amounts of human chorionic gonadotrophin (HCG) may stimulate the thyroid to produce thyrotoxicosis (Higgins *et al.*, 1975; Kenimer *et al.*, 1975). Although hyperthyroidism may present for the first time during pregnancy, it may well represent a relapse of pre-existing Graves' disease hitherto in remission. We shall also consider the problem of the woman with previous Graves' disease who is euthyroid, either because she is in remission or is being maintained on anti-thyroid medication or because she has had a thyroidectomy.

Hyperthyroidism is often a difficult diagnosis to establish in pregnant women because symptoms due to a hyperdynamic circulation occur normally and the thyroid gland frequently enlarges in normal women during pregnancy. Specific clinical clues suggesting hyperthyroidism in pregnancy include a loss of weight despite a maintained appetite, persistent and marked increase in pulse rate, together with physical findings such as the presence of a bruit in a goitre and the development of eye signs or pretibial myxoedema.

Definitive diagnosis requires biochemical confirmation and since pregnancy precludes the use of *in vivo* isotopic studies, *in vitro* tests of thyroid function are required. Because of the changes in thyroxine binding globulin during pregnancy it is essential either to measure the free thyroxine concentration directly or to obtain an index of the free thyroxine.

Untreated hyperthyroidism is a serious hazard to the fetus (Serup, 1979; Montoro and Mestman, 1981b). The major risks are abortion, premature

labour and neonatal thyrotoxicosis, the last being due to transplacental passage of thyroid-stimulating immunoglobulin (Munro *et al.*, 1978). This condition is particularly important because it does not depend upon the maternal thyroid status and it is therefore a risk that must be carefully evaluated, even in the euthyroid woman with a past history of Graves' disease who is presently in remission. It is at present uncertain however whether fetal (that is, intrauterine) thyrotoxicosis actually occurs and certainly the fetus has a poor capacity to convert thyroxine to tri-iodothyronine (metabolically the most active form of thyroid hormone) until just before term (Fisher and Klein, 1981).

Maternal weight loss due to thyrotoxicosis must be avoided since the underweight mother is more likely to deliver a small-for-dates baby—especially if her pregnancy weight gain is poor (Edwards *et al.*, 1979; Niswander and Jackson, 1974). The fetus of the thyrotoxic woman who is receiving treatment with anti-thyroid medication is also at risk, since carbimazole, propylthiouracil and iodide all readily cross the placenta and inhibit fetal thyroid hormone secretion (Roti, Gnudi and Braverman, 1983). Data incriminating long-term consequences of fetal hypothyroidism (as opposed to those incriminating neonatal hypothyroidism) are in fact scanty, although severely hypothyroid neonates have markedly impaired bone maturation [reversible on post natal treatment with thyroxine (Hulse *et al.*, 1982)], and, of course, the development of a fetal goitre detectable by ultrasound may prejudice the outcome of labour.

The objective of treatment of the hyperthyroid pregnant woman is to induce euthyroidism in the mother at minimal risk to the fetus. Treatment with radio-iodine is precluded and surgery is best avoided unless the patient proves resistant or allergic to conventional medical treatment. So far as drug treatment is concerned, there is a debate about the optimum regimen. Some endocrinologists use carbimazole (Ramsay, Kaur and Krassas, 1983) while others prefer propylthiouracil (Cheron *et al.*, 1981; Solomon, 1981), the latter particularly because it is said to be associated with a lower prevalence of blood dyscrasias and also because, in addition to its action on the thyroid gland, it inhibits the peripheral conversion of thyroxine to tri-iodothyronine and so has a more rapid onset of action than carbimazole.

We recommend that treatment is initiated either with carbimazole, in a dose of 15 mg three times per day or with propylthiouracil, in a dose of 150 mg three times per day, reducing after about 6 weeks to 10 mg and 100 mg three times per day respectively for 6 weeks and thence to maintenance doses of 10–20 mg of carbimazole or 100–200 mg of propylthiouracil in divided doses per day. Although biochemi-

cal changes can be detected in the cord blood of infants of mothers treated with propylthiouracil, fetal goitre is unusual when the maintenance dose remains below 200 mg a day and the infants are clinically euthyroid (Burrow, 1978; Cheron *et al.*, 1981). Furthermore the intellectual development of children exposed to transplacental propylthiouracil appears to be unimpaired (Burrow, Klatskin and Genel, 1978).

Some physicians recommend that thyroxine is added to the anti-thyroid medication. While little of the maternal thyroxine crosses the placenta at a biologically significant rate, it must be accepted that there are data suggesting that combined treatment reduces the incidence of fetal goitre (Ramsay *et al.*, 1983). Controlled clinical trials have not however been performed and the results could also be attributed to different patterns of disease and different dose schedules in the various groups. Until such trials have been reported, we recommend treatment with propylthiouracil or carbimazole alone, given in the lowest doses that keep the mother asymptomatic, the maternal pulse rate below 90/min and the free thyroxine concentration (or index) within the normal range. We assess these patients clinically, and with measurements of the free thyroxine concentration, at 1–2 weekly intervals until they are euthyroid and then at 4 weekly intervals until delivery. We reserve treatment with beta adrenergic blockers, which can have adverse effects on the fetal cardiovascular system (Dumez *et al.*, 1981), and with iodine for the rare patient who develops a thyroid crisis during pregnancy or the patient in whom a crisis is precipitated by delivery before the condition is under control (Jacobs *et al.*, 1973; Burrows, 1978; Serup, 1979; Edwards, 1979).

In most cases the patient's goitre will get smaller as treatment brings the hyperthyroidism under control. Enlargement may occur either because the patient has been over treated or because of worsening of the basic disease. In the former case, plasma TSH levels will have risen, and free thyroxine may have fallen, and reduction of the dose of anti-thyroid drug should cause the goitre to recede. If the thyroid condition is deteriorating (plasma-free thyroxine concentrations remain high despite large amounts of anti-thyroid medication) the patient should be considered for thyroidectomy, preferably performed in the second trimester.

Although labour and delivery are times of stress, Caesarean section and obstetric intervention are only indicated for conventional obstetric reasons. Oxytocin infusion is not contra-indicated but sympathomimetic drugs for the control of pre-term labour should be avoided. Should the patient's condition worsen during labour, propranolol (40–120 mg qds) and potassium iodide (60 mg tds) may be given since this

is a short-lived situation in which delivery is imminent. In women who have been on anti-thyroid medication during pregnancy, the attitude of the fetal head must be carefully observed because a large fetal goitre may extend the neck and result in a brow presentation and cephalo-pelvic disproportion. In these cases, delivery by Caesarean section is necessary, preferably with epidural anaesthesia but failing this, a general anaesthetic may be administered by an experienced anaesthetist (Komins *et al.*, 1975).

Thyroid function in the neonate should be carefully assessed by measurement of thyroxine and TSH concentrations in cord blood. Hypothyroidism induced by propylthiouracil is usually transitory and lasts 1–2 weeks. If the neonatal T_4 is low (less than 60 nmol/l) or the TSH high (more than 20 mU/l), careful assessment by the paediatricians is advised. Since propylthiouracil is rapidly eliminated from the fetus, treatment is usually not required.

After delivery and in the puerperium, the mother's thyroid function should be monitored and treatment adjusted according to the results. Day 8 post-partum, the 6-week post-partum visit and 4 months after delivery are the appropriate times for reassessment of thyroid function. In our opinion, puerperal patients receiving propylthiouracil may breast feed since only about 0.025% of the ingested dose appears in the milk, which gives a dose of propylthiouracil to the baby of less than 0.5 mg per day, an amount extremely unlikely to affect the baby's thyroid function (Kampmann *et al.*, 1980). Contraception with the combined oral contraceptive pill is not contra-indicated in these patients.

Transient post-partum thyroid disease

A number of reports have recently described transient hypo- and hyperthyroidism following delivery (Ginsberg and Walfish, 1977; Amino *et al.*, 1977; Hoffbrand and Webb, 1978). These patients often have a pre-existing goitre, associated with circulating microsomal thyroid autoantibodies. While transient hyperthyroidism usually occurs within 2 months of delivery, hypothyroidism usually develops 4–6 months afterwards. The patient may go through a hyperthyroid phase only to develop hypothyroidism subsequently and it is important to realise that both conditions, either occurring separately or sequentially, usually remit spontaneously. We have seen three such patients in the last year and describe here a representative case history.

A 27-year-old woman delivered her first child in March 1982. Ten weeks post-partum she presented complaining of restlessness, palpitation, heat intolerance and weight loss despite a maintained appetite.

FIG. 1. TSH, T_3 , free thyroxine, and thyroxine measurements in woman with post-partum thyroid disease in the year following delivery.

Thyroid function tests confirmed the clinical diagnosis of hyperthyroidism and she was found to have microsomal thyroid autoantibodies (160%). Figure 1 demonstrates the course her thyroid disease took. As can be seen, she was initially thyrotoxic, then became hypothyroid but 7 months after initial assessment all parameters of thyroid function had returned to normal. She received no treatment during the year of follow-up.

The aetiology is likely to be autoimmune because of the similarity of many of the features of this syndrome (low radioiodine uptake but normal technetium-99 uptake, lymphocytic infiltration of the thyroid, circulating auto-antibodies, relationship to HLA genotype) with those of the syndrome of silent thyrotoxic thyroiditis (Klein and Levey, 1982). The mechanism of the pregnancy-related disturbance is unknown but the clinical importance is that a diagnosis of either hyper- or hypothyroidism in the puerperium is not necessarily an indication for immediate or long-term treatment because of the tendency of both conditions to remit spontaneously. The condition is particularly common in Japan and North America where it has been reported in up to 5% of post-partum women (Amino *et al.*, 1982).

Neonatal period

A number of babies born to mothers with Graves disease, either active or in the past, may develop neonatal thyrotoxicosis (Ramsay, 1980; Ramsay

FIG. 2. Neonatal thyrotoxicosis (by courtesy of Dr S. McHardy Young).

al., 1983). These infants show failure to thrive either because of poor eating or in association with a voracious appetite, and diarrhoea is a frequent symptom. They are often hyperkinetic and have a tachycardia, together with goitre and occasionally eye signs (Fig. 2). Infections associated with thyroid crisis, cardiac symptoms and tracheal obstruction secondary to large goitre are the most serious threats to life. The thyrotoxicosis is usually transient lasting less than 6 months in most cases and is caused by stimulation of the fetal thyroid by maternally-transmitted thyroid-stimulating immunoglobulins (McKenzie, 1964; Hollingsworth and Mabry, 1975). Even euthyroid patients with a past history of Graves' disease may deliver babies that develop transient thyrotoxicosis, so obstetricians should be on the alert for this condition and the risks should be

considered, especially when the mother has had marked eye signs and/or pre-tibial myxoedema. The condition is more probable if the maternal LATS-P concentration is greater than 20 u/ml (Dirmikis and Munro, 1975). Cord blood should be obtained and measurements of T_4 , free thyroxine concentrations (or index) and T_3 concentrations obtained and the infant should be treated promptly with appropriate doses of anti-thyroid drugs in a specialist paediatric endocrine unit. In a small proportion of these children, the disease will have a prolonged course and require long-term therapy (Hollingsworth and Mabry, 1975).

Parathyroid

The increased calcium demands of pregnancy are met by enhanced calcium absorption from the gut, mediated by an increase of 1,25 dihydroxy cholecalciferol (the active metabolite of vitamin D). The tendency of 1,25 dihydroxy cholecalciferol to cause reabsorption of bone is however opposed by the increased secretion of calcitonin (Austin and Heath, 1981), so calcium is provided to the fetus from the maternal gut rather than from the maternal skeleton (Whitehead *et al.*, 1981; Heaney and Skillman, 1971). The increased calcitonin secretion is probably stimulated by the oestrogens of pregnancy and enhanced production of the active metabolite of vitamin D is possibly mediated through placental lactogen and prolactin (Kumar *et al.*, 1979). It is unlikely that there are any major changes in parathyroid hormone (PTH) secretion during pregnancy.

Hyperparathyroidism

About 70 cases of hyperparathyroidism have been reported in pregnant women (Montoro and Mestman, 1981a). Although the condition itself does not impair fertility, infertility may be caused by hyperprolactinaemia if the hyperparathyroidism is part of the pluriglandular syndrome. The condition should be suspected whenever a raised serum calcium concentration is found on routine screening, but some cases have only been diagnosed post-partum when neonatal tetany has developed. Forty to fifty percent of pregnant patients present with renal stones. There may be gastrointestinal symptoms, with fatigue, muscle weakness, weight loss, arthralgia or psychiatric problems. A history of a previous infant with neonatal tetany is clearly important. In 80% of cases there is a small adenoma but in 15% the cause is hyperplasia of all four glands. A few cases are caused by either multiple adenomas or by parathyroid carcinoma. In the United States, a significant proportion of the cases of hyperparathyroidism (10–37% of cases reported in some centres)

TABLE 2. Hyperparathyroidism in pregnancy—effect of parathyroidectomy (Deutsch *et al.*, 1980)

Method of treatment	Number of:		Normal births	Fetal/neonatal complications
	Women	Pregnancies		
Surgical	10	10	8	2
Non-surgical	33	52	21	31
Total	43	62	29	33

have followed irradiation of the neck in childhood (Aurbach, Marx and Spiegel, 1981).

The diagnosis is made by finding persistently elevated serum calcium concentrations associated with PTH concentrations that have not been suppressed. Twenty-four hour urinary calcium is usually raised. The usual diagnostic approach to hypercalcaemia used in non-pregnant women should be undertaken (Aurbach *et al.*, 1981). In untreated pregnant patients the fetal outcome is very poor, with up to a 50% pregnancy loss through abortion, intrauterine death, premature delivery or neonatal tetany. Possibly the raised serum calcium levels of the mother cause prolonged intrauterine depression of the fetal parathyroid gland, which in turn causes neonatal hypocalcaemia and tetany (Delmonico *et al.*, 1976).

In recent years, management of these patients has tended to favour parathyroid surgery during pregnancy (Deutsch *et al.*, 1980). Table 2, taken from the report of Deutsch *et al.*, shows that the results in terms of fetal salvage are dramatically improved following surgical treatment compared with those in women treated conservatively. If possible surgery should be performed in the second trimester. It is a technically demanding operation, particularly during pregnancy, and a special risk is haemorrhage which may occur post-operatively with subsequent airways obstruction. So far as the pregnancy is concerned, normal labour, delivery and lactation are allowed.

In women with hyperparathyroidism there are often associated endocrine disorders—diabetes, thyroid disease, Cushing's syndrome, acromegaly and carcinoid have all been reported and each obviously requires special management (Hamilton and Pryor, 1981). Seven to ten percent of non-pregnant patients present simultaneously with pancreatitis and hyperparathyroidism. This association should therefore be considered in the differential diagnosis of a pregnant woman with an acute abdomen (Thomason *et al.*, 1981). Finally, it is important to remember that patients with hyperparathyroidism may present in pregnancy dehydrated, with polyuria, nausea, vomiting and central nervous system depression. The serum calcium concentration is very high. The treatment is by active rehydration and restoration of

electrolyte balance with intravenous saline. Frusemide, oral phosphate and calcitonin (Defetos and First, 1981), may be given if the calcium levels remain high despite rehydration and dialysis may be necessary in very severe, persistent and symptomatic hypercalcaemia. Surgery is indicated after the condition has stabilized (Clark, Seeds and Cefalo, 1981). There are no special problems concerning lactation or contraception in these patients.

The neonate should be assessed for hypocalcaemia, initially with measurements of serum calcium and inorganic phosphate in cord blood. Neonatal hypocalcaemia usually responds to the addition of calcium salts to the feeds for 1–2 weeks, but this requires specialized paediatric supervision.

Hypoparathyroidism

Hypoparathyroidism may be caused by peripheral hormone resistance (pseudo-hypoparathyroidism) or by deficient parathyroid hormone production. The latter occurs in 0.2–3.5% of post-thyroidectomy patients. Auto-immune endocrine disorders such as Addison's disease of the adrenal or primary ovarian failure are often associated with idiopathic hypoparathyroidism. Clinically patients with hypoparathyroidism may be clumsy, they may convulse and they often complain of stiffness and paraesthesia and they may have laryngeal stridor or tetany. The skin is dry and scaly and they have brittle nails and coarse hair. Calcification in soft tissues may occur and Chvostek and Trousseau's signs are positive. Both serum calcium and parathyroid hormone concentrations are low. Diagnosis is made on the history and on the plasma biochemistry.

If this condition remains untreated, there is a high fetal and maternal mortality. The prognosis with treatment is good provided the patient remains normocalcaemic. Treatment consists of vitamin D₃ given in the form of the synthetic analogue dihydroxytachysterol, in a dose of 250–1,000 µg per day together with 1–2 g of elemental calcium per day. Serum calcium levels should be monitored throughout pregnancy (Montoro *et al.*, 1981a). Should a hypocalcaemic crisis develop (severe tetany, laryngeal spasm, or convulsions) it is treated with a slow

intravenous injection of calcium—that is 10–20 ml of 10% calcium gluconate given at the rate of 10 ml/min and thereafter by constant infusion—10 ml of 10% calcium gluconate added to 500 ml of fluid and given over 6 hr. If this therapy does not bring rapid improvement, the serum magnesium concentrations should be checked and if sub-normal, the patient given magnesium sulphate, 2 ml of a 50% solution being given intramuscularly 8–12 hourly as necessary (Montoro *et al.*, 1981a).

The dose of vitamin D should be reassessed in the post-partum period. The mother frequently requires no treatment at this stage (Wright, Joplin and Dixon, 1969). Breast feeding is contra-indicated because vitamin D is secreted into the milk and may cause hypervitaminosis in infants.

Acknowledgment

We should like to thank Dr Stuart McHardy Young of the Central Middlesex Hospital for permission to publish the photograph of his patient shown in Fig. 2.

References

- AMINO, N., MIYAI, K., KURO, R., TANIZAWA, O., AZUKIZAWA, M., TAKAI, S., TANAKA, F., NISHI, K., KAWASHIMA, M. & KUMAHARA, Y. (1977) Transient post-partum hypothyroidism: Fourteen cases with auto-immune thyroiditis. *Annals of Internal Medicine*, **87**, 155.
- AMINO, N., MORI, H., IWATANI, Y., TANIZAWA, O., KAWASHIMA, M., TSUGE, I., IBARAGI, K., KUMAHARA, Y. & MIYAI, K. (1982) High prevalence of transient post-partum thyrotoxicosis and hypothyroidism. *New England Journal of Medicine*, **306**, 849.
- AURBACH, G.D., MARX, S.J. & SPIEGEL, A.M. (1981) Parathyroid hormone, calcitonin and the calciferols. In: *Textbook of Endocrinology* (Ed. R. H. Williams), 6th edn., p. 922. W. B. Saunders and Company, Philadelphia, London, Toronto.
- AUSTIN, L.A. & HEATH, H. (1981) Calcitonin. Physiology and pathophysiology. *New England Journal of Medicine*, **304**, 269.
- BURROW, G.N. (1978) Hyperthyroidism during pregnancy. *New England Journal of Medicine*, **298**, 150.
- BURROW, G.N., KLATSKIN, E.H. & GENEL, M. (1978) Intellectual development in children whose mothers received propylthiouracil during pregnancy. *Yale Journal of Biology and Medicine*, **51**, 151.
- CHERON, R.G., KAPLAN, M.M., LARSEN, P.R., SELENKOW, H.A. & CRIGLER, J.F. (1981) Neonatal thyroid function after propylthiouracil therapy for maternal Graves' disease. *New England Journal of Medicine*, **304**, 525.
- CLARK, D., SEEDS, J.W. & CEFALO, R.C. (1981) Hyperparathyroid crisis and pregnancy. *American Journal of Obstetrics and Gynecology*, **140**, 840.
- DEFTOS, L.J. & FIRST, B.P. (1981) Calcitonin as a drug. *Annals of Internal Medicine*, **95**, 192.
- DELMONICO, F.L., NEER, R.M., COSIMI, A.B., BARNES, A.B. & RUSSELL, P.S. (1976) Hyperparathyroidism during pregnancy. *American Journal of Surgery*, **131**, 328.
- DEUTSCH, A.A., ZAGER, M., BERNHEIM, J., STEINER, Z. & REISS, R. (1980) The diagnosis and management of hyperparathyroidism during pregnancy. *Postgraduate Medical Journal*, **56**, 333.
- DIRMIKIS, S.M. & MUNRO, D.S. (1975) Placental transmission of thyroid-stimulating immunoglobulins. *British Medical Journal*, **2**, 665.
- DUMEZ, Y., TCHOBRUTSKY, C., HORNYCH, H. & AMIEL-TISON, C. (1981) Neonatal effects of maternal administration of acebutolol. *British Medical Journal*, **283**, 1077.
- EDITORIAL (1972) New light on endemic cretinism. *Lancet*, **ii**, 365.
- EDWARDS, L.E., ALTON, I.R., BARRADA, M.I. & HAKANSON, E.Y. (1979) Pregnancy in the underweight woman. Course, outcome and growth patterns of the infant. *American Journal of Obstetrics and Gynecology*, **135**, 297.
- EDWARDS, O.M. (1979) The management of thyroid disease in pregnancy. *Postgraduate Medical Journal*, **55**, 340.
- EKINS, R.P. (1979) Methods for the measurement of free thyroid hormones. In: *Free thyroid hormones, Proceedings of the international symposium held in Venice, December 1978*. (Eds. R. Ekins, G. Faglia, F. Pennisi and A. Pinchera), p. 72. Excerpta Medica, Amsterdam, Oxford, Princeton.
- FISHER, D.A. (1975) Thyroid function in the fetus. In: *Perinatal thyroid physiology and disease* (Eds. D. A. Fisher and G. N. Burrow), p. 21. Raven Press, New York.
- FISHER, D.A. & KLEIN, A.H. (1981) Thyroid development and disorders of thyroid function in the newborn. *New England Journal of Medicine*, **304**, 702.
- GINSBERG, J. & WALFISH, P.G. (1977) Post-partum transient thyrotoxicosis with painless thyroiditis. *Lancet*, **i**, 1125.
- HAMILTON, D.V. & PRYOR, J.S. (1981) Endocrine abnormalities in primary hyperparathyroidism. *Postgraduate Medical Journal*, **57**, 167.
- HEANEY, R.P. & SKILLMAN, T.G. (1971) Calcium metabolism in normal human pregnancy. *Journal of Clinical Endocrinology and Metabolism*, **33**, 661.
- HIGGINS, H.P., HERSHMAN, J.M., KENIMER, J.G., PATILLO, R.A., BAYLEY, T.A. & WALFISH, P. (1975) The thyrotoxicosis of hydatidiform mole. *Annals of Internal Medicine*, **83**, 307.
- HOFFBRAND, B.I. & WEBB, S.C. (1978) Post-partum thyroiditis. *Postgraduate Medical Journal*, **54**, 793.
- HOLLINGSWORTH, D.R. & MABRY, C.C. (1975) Congenital Graves' disease. In: *Perinatal Thyroid Physiology and Disease* (Eds. D. A. Fisher and G. N. Burrows), p. 163. Raven Press New York.
- HULSE, J.A., GRANT, D.B., JACKSON, D. & CLAYTON, B.E. (1982) Growth, development and reassessment of hypothyroid infants diagnosed by screening. *British Medical Journal*, **284**, 1435.
- INGBAR, S.H. & WOEBER, K.A. (1981) The thyroid gland. In: *Textbook of Endocrinology* (Ed. R. H. Williams), 6th edn., p. 117. W. B. Saunders and Company, Philadelphia, London, Toronto.
- JACOBS, H.S., MACKIE, D.B., EASTMAN, C.J., ELLIS, S.M., EKINS, R.P. & MCHARDY-YOUNG, S. (1973) Total and free tri-iodothyronine and thyroxine levels in thyroid storm and recurrent hyperthyroidism. *Lancet*, **ii**, 236.
- KAMPFANN, J.P., JOHANSEN, K., HANSEN, J.M. & HELWEG, J. (1980) Propylthiouracil in human milk. *Lancet*, **i**, 736.
- KENIMER, J.G., HERSHMAN, J.M. & HIGGINS, H.P. (1975) The thyrotropin in hydatiform moles is human chorionic gonadotrophin. *Journal of Clinical Endocrinology and Metabolism*, **40**, 482.
- KLEIN, I. & LEVEY, G.S. (1982) Silent thyrotoxic thyroiditis. *Annals of Internal Medicine*, **96**, 242.
- KLEIN, R.Z. (1979) Neonatal screening for hypothyroidism. In: *Advances in Pediatrics*, Vol. 26 (Ed. L. A. Barnes), p. 417. Year Book Publishers, Chicago, London.
- KOMINS, J.I., SNYDER, P.J. & SCHWARZ, R.H. (1975) Hyperthyroidism in pregnancy. *Obstetrical and Gynecological Survey*, **30**, 527.
- KUMAR, R., COHEN, W.R., SILVA, P. & EPSTEIN, F.H. (1979) Elevated 1,25-dihydroxy-vitamin D plasma levels in normal human pregnancy and lactation. *Journal of Clinical Investigation*, **63**, 342.
- MCKENZIE, J.M. (1964) Neonatal Graves' disease. *Journal of Clinical Endocrinology and Metabolism*, **24**, 660.
- MONTORO, M., COLLEA, J.V., FRASIER, S.D. & MESTMAN, J.H. (1981) Successful outcome of pregnancy in women with hypothyroidism. *Annals of Internal Medicine*, **94**, 31.
- MONTORO, M. & MESTMAN, J.H. (1981a) How to manage parathyroid disease in the pregnant patient and neonate. *Contemporary Obstetrics and Gynecology*, **17**, 143.
- MONTORO, M. & MESTMAN, J.H. (1981b) Graves' disease and pregnancy. *New England Journal of Medicine*, **305**, 48.

- MUNRO, D.S., DIRMİKIS, S.M., HUMPHRIES, H., SMITH, T. & BROADHEAD, G.D. (1978) The role of thyroid stimulating immunoglobulins of Graves's disease in neonatal thyrotoxicosis. *British Journal of Obstetrics and Gynaecology*, **85**, 837.
- NISWANDER, K. & JACKSON, E.C. (1974) Physical characteristics of the gravida and their association with birthweight and perinatal death. *American Journal of Obstetrics and Gynecology*, **119**, 306.
- PHAROAH, P., CONNOLLY, K., HETZEL, B. & EKINS, R. (1981) Maternal thyroid function and motor competence in the child. *Developmental Medicine and Child Neurology*, **23**, 76.
- RAMSAY, I. (1980) Thyroid disease in pregnancy. *Hospital Update*, **6**, 685.
- RAMSAY, I., KAUR, S. & KRASSAS, G. (1983) Thyrotoxicosis in pregnancy: results of treatment by antithyroid drugs combined with T4. *Clinical Endocrinology*, **18**, 73.
- ROTI, E., GNUDI, A. & BRAVERMAN, L.E. (1983) The placental transport synthesis and metabolism of hormones and drugs which affect thyroid function. *Endocrine Reviews*, **4**, 131.
- SERUP, J. (1979) Pregnancy and birth associated with thyrotoxicosis. *Danish Medical Bulletin*, **26**, 74.
- SOLOMON, D.H. (1981) Pregnancy and PTU. *New England Journal of Medicine*, **304**, 538.
- SMITH, S.C.H. & BOLD, A.M. (1983) Interpretation of in vitro thyroid function tests during pregnancy. *British Journal of Obstetrics and Gynaecology*, **90**, 532.
- THOMASON, J.L., SAMPSON, M.B., FARB, H.F. & SPELLACY, W.J. (1981) Pregnancy complicated by concurrent primary hyperparathyroidism and pancreatitis. *Obstetrics and Gynaecology*, **57**, 345.
- WHITEHEAD, M., LANE, G., YOUNG, O., CAMPBELL, S., ABEYASEKERA, G., HILLYARD, C.J., MACINTYRE, I., PHANG, K.G. & STEVENSON, J.C. (1981) Interrelations of calcium-regulating hormones during normal pregnancy. *British Medical Journal*, **283**, 10.
- WRIGHT, A.D., JOPLIN, G.F. & DIXON, H.G. (1969) Post-partum hypercalcaemia in treated hypoparathyroidism. *British Medical Journal*, **1**, 23.
- YAMAMOTO, T., AMINO, N., TANIZAWA, O., DOI, K., ICHIHARA, K., AZUKIZAWA, M. & MIYAI, K. (1979) Longitudinal study of serum thyroid hormones, chorionic gonadotrophin and thyrotrophin during and after normal pregnancy. *Clinical Endocrinology*, **10**, 459.

(Received 3 October 1983)