THYROID DISEASE IN PREGNANCY

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INTRODUCTION

THE recognition of thyroid dysfunction in pregnancy is important for the welfare of both mother and fetus. Obstetricians tend to think of the thyroid disease as complicating the pregnancy, whereas physicians look at it the other way round. Both viewpoints must be taken into consideration for neither condition can be treated successfully if the other is neglected. The knowledge of how the thyroid disease is affected by the pregnancy, and how the disease and its treatment influences pregnancy and fetal development, is essential in determining the management of these patients.

The purpose of this paper is to review the changes that occur in thyroid physiology in pregnancy and to report the extent of thyroid disease seen in pregnancy in the Royal Maternity Hospital, Belfast, over a 16-year period, 1963 to 1978.

MATERNAL AND FETAL THYROID FUNCTION IN PREGNANCY

Maternal Factors

The physiological changes which occur in thyroid metabolism in pregnancy have been reviewed by Selenkow et al (1973) and Tunbridge and Hall (1975). Information on the interrelationship of maternal and fetal thyroid activity is still incomplete, but some facts are fairly well known.

The BMR rises in pregnancy but this is mainly due to extrathyroidal factors. The protein-bound iodine level is elevated as a result of increased thyroxine binding capacity of the plasma protein, brought about by the secretion of oestrogens during pregnancy. There is an increase in the renal clearance of iodide which is associated with a lowering of the plasma inorganic iodine level. The thyroid clearance of iodine and its uptake of radio-iodine are thus raised to make up for the renal loss of iodide and the gland enlarges in response. This has an important clinical application for it means that thyroid enlargement in pregnancy *per se* is not necessarily due to a pathological process.

The placenta has been shown to secrete a thyroid stimulating factor called human chorionic thyrotrophin. This may explain why the thyroid stimulating activity of the plasma is greater in pregnant than in non-pregnant women and it provides a further reason for the enlargement of the thyroid in pregnancy. Recent evidence suggests human chorionic gonadotrophin may be the chorionic thyrotrophin referred to. The activity of one IU of human chorionic gonadotrophin is equivalent to 0.5μU of human TSH (Kenimer et al, 1975). However, the role, if any, of this placental thyroid stimulator in the regulation of thyroid

function in pregnancy is far from clear. The response of TSH to TRH is increased in pregnancy and is likely to be due to the enhanced sensitivity of the pituitary thyrotroph cell brought about by the increased secretion of oestrogens.

Although the level of PBI, total T_4 and total T_3 rise in pregnancy it must be remembered that it is not the bound but the free hormones which take part in physiological processes. In pregnancy, the free T_4 and T_3 levels remain stable and similar to those in non-pregnant controls and the rate of hormone production and degradation is unaltered. Similarly, serum TSH values remain normal during pregnancy. For these reasons one must conclude that the normal woman is euthyroid throughout her pregnancy.

Fetal Factors

Not much is known about fetal thyroid metabolism. The earliest date that iodinated proteins have been recovered from the thyroid is at the tenth week of gestation and thyroxine is detectable in the serum by the eleventh week. This means that, for the first 10 to 12 weeks or so of intrauterine life, the fetus has no competent functioning thyroid tissue and must, presumably, depend on maternal sources for thyroid hormone, if such is necessary for early development. During the second trimester the fetal thyroid starts to synthesize hormone but the activity of the gland is relatively low. The normal pituitary-thyroid axis is established by the fourth or fifth month of gestation.

In the second trimester fetal PBI and total T_4 concentrations are in the adult hypothyroid range. However, since fetal thyroid binding protein is also low, free T_4 values are similar to those in the maternal circulation. By the end of pregnancy, the fetal PBI, total T_4 and thyroid binding protein are almost equal to maternal levels. In contrast, fetal T_3 levels are low before 24 weeks and while they rise subsequently they remain much lower than maternal levels even at term (Fisher et al, 1973). The concentration of thyroxine in amniotic fluid remains relatively constant throughout pregnancy but triiodothyronine levels are undetectable. Unexpectedly high values of reversed T_3 (3, 3′, 5′-triiodothyronine, rT_3), a hormone with little biological effect, are found between 15 to 30 weeks but decrease substantially thereafter. Mean thyroxine and T_3 values in amniotic fluid are lower and rT_3 levels are higher than the corresponding values in maternal serum (Chopra and Crandall, 1975). The significance of the high concentration of rT_3 in amniotic fluid is not known.

At birth, cord T_3 levels are low while rT_3 levels are raised. In the hours after birth serum T_3 concentrations rise 200 to 400 per cent while T_4 values rise 25 to 50 per cent. The increase in T_4 and part of the T_3 rise is due to the transient neonatal increase in TSH secretion. However, most of the rise in T_3 must be due to a rapid postnatal increase in extrathyroidal conversion of T_4 to T_3.

The rate and extent of thyroid hormone transfer across the placenta remains unsettled. There is evidence that free thyroxine will pass from mother to fetus and that T_3 is slightly more permeable, but the degree of transfer is low (Selenkow et al, 1973). The reverse situation in which fetal thyroid hormone

reaches the mother is even less well known. In a case of maternal hypothyroidism which we observed, the maternal T_4 and T_3 values rose, while TSH levels fell to near normal as the pregnancy proceeded, presumably as the result of transplacental passage of hormone from fetus to mother. After delivery, the mother rapidly became hypothyroid again (Kennedy and Montgomery, 1978). The thyroid stimulating immunoglobulins, the immunoglobulins associated with Graves' disease cross the placenta quite easily.

THYROID DISEASE IN PREGNANCY

Table I records the occurrence of thyroid disease observed in the Royal Maternity Hospital from January 1963 to November 1978.

TABLE I

Thyroid disease in pregnancy. Royal Maternity Hospital, Belfast 1963-78.

HYPERTHYROIDISM		73
Treated medically	68*	
Treated surgically	3	
No treatment	2*	
HYPOTHYROIDISM		64†
NON-TOXIC GOITRE		59
Diffuse gland	39	
Nodular gland	20	
MISCELLANEOUS THYROID DISEASE		112
Total pregnancies		308

* Includes two cases of T_3 thyrotoxicosis.

† Includes two cases of untreated hypothyroidism.

Sixty-eight had their thyrotoxicosis treated with antithyroid drugs while thyroidectomy was performed in three. Two patients were untreated because they were seen late in pregnancy. Sixty-four pregnancies occurred in hypothyroid mothers. All but two were maintained in an euthyroid state with thyroxine during the time they were under observation. In fifty-nine pregnancies a non-toxic goitre was present. One hundred and twelve of the remaining pregnancies were associated with miscellaneous forms of thyroid disease (Table II). Forty and thirty-four had had previous medical or surgical treatment for thyrotoxicosis and were euthyroid during their pregnancies. Seventeen had a thyroid cyst, nodule or simple goitre removed earlier. A previous thyroiditis occurred in eight, and ten women with carcinoma of the thyroid treated by total or subtotal thyroidectomy had thirteen pregnancies between them. In one, the papilliary carcinoma was first recognized in pregnancy and it was removed surgically at the nineteenth week of gestation.

A previous history of thyroid disease indicates the presence of a diseased or imperfect gland which may not be able to support the metabolic demands of pregnancy. Hence, it is important to decide if the mother is euthyroid and to monitor thyroid function throughout pregnancy.

TABLE II

Miscellaneous forms of thyroid disease. Royal Maternity Hospital, Belfast 1963-78.

Previous medical treatment for Graves' disease	40
Previous thyroidectomy for Graves' disease	34
Previous removal of thyroid cyst or nodule or simple goitre	17
Thyroiditis	8
Carcinoma of thyroid	13
Total number of pregnancies	112

PREGNANCY AND HYPERTHYROIDISM

Hyperthyroidism complicates pregnancy in approximately 0.2 per cent of cases (0.18 per cent in this series). Most commonly it results from Graves' disease, but toxic nodular goitre is sometimes the cause. Usually the thyrotoxicosis antedates conception and the latter follows when the hyperthyroid state has been brought under control by treatment. Fertility is impaired and rates of abortion are higher in the untreated thyrotoxic than in normal women.

The diagnosis of hyperthyroidism in pregnancy is often difficult, especially in milder cases, because physiological changes may mimic closely the features of hyperthyroidism. Biochemical investigations may also be confusing because of the changes in thyroid tests brought about by increases in thyroid binding proteins. Pregnancy appears to ameliorate, to some extent, the severity of the thyrotoxicosis so that clinical features may be mild. Radioactive iodine tests administered to the mother must be avoided and reliance placed on the measurement of T_4, T_3 and TSH. Circulating levels of total T_4 and T_3 rise in pregnancy and, as the measurement of free (unbound) T_4 and T_3 is technically difficult and usually not available, most reliance is placed on the free thyroxine index (FTI) using the Thyopac-3 and Thyopac-4 kits (Radiochemical Centre, Amersham). The normal pregnancy value of 90 ± 17 is not far different from the non-pregnant control level of 84 ± 21 and all euthyroid pregnant women fall in the normal range (Bell et al, 1974). A similar free triiodothyronine index can be obtained by using the Thyopac-3 result. The T_3 red cell or resin uptake test performed *in vitro* is also useful. In normal pregnancy the uptake is in the hypothyroid range. In the thyrotoxic patient levels are usually in the low normal range. The occurrence of T_3 thyrotoxicosis in pregnancy will be missed if T_3 values are not measured routinely, because the usual tests are unaltered in this form of hyperthyroidism.

In spite of the help offered by laboratory investigations the diagnosis of hyperthyroidism in pregnancy remains largely clinical. Reliance must be placed

on features such as loss of weight, or failure to gain weight in the presence of a good appetite, a high sleeping pulse rate, a significant goitre with increased blood flow and the eye signs found in Graves' disease, such as periorbital swelling, lid retraction and exophthalmos.

Treatment of thyrotoxicosis during pregnancy demands special care because both disease and treatment carry special risks. The choice lies between antithyroid drugs with or without thyroid hormone supplements and subtotal thyroidectomy (Werner, 1967). Both have their proponents (Becker and Sudduth, 1959; Hawe and Francis, 1962; Herbst and Selenkow, 1965; Talbert et al, 1970; Selenkow et al, 1973; Goluboff et al, 1974). The choice between antithyroid drug treatment and surgery is made on several grounds and need not be influenced unduly by the pregnancy.

Subtotal thyroidectomy is indicated for patients with large goitres causing obstruction, or those whose thyrotoxicosis cannot be controlled by reasonably modest doses of antithyroid drugs (under 300 mg of propylthiouracil or 30 mg of carbimazole daily) or who manifest toxic reactions to antithyroid drugs, or for those who are unwilling to or unable to follow the medical regimen correctly. During the first two trimesters a thyroidectomy performed after suitable preparation causes little risk to the fetus, but during the last trimester an operation may precipitate labour and for this reason antithyroid drug treatment is often preferred. Preoperative treatment must be suited to each patient's needs using antithyroid drugs, iodides and propranolol to render the patient euthyroid. Prolonged treatment with iodides (more than two weeks) must be avoided because of the risk of goitre formation in the fetus. Instead, the beta-adrenergic blocking drug propranolol may be used to control the peripheral manifestations of the disease. Postoperatively it is advisable to put the patient on full doses of thyroxine replacement if the TSH level rises, and to reassess the need for continuing therapy after delivery (Tunbridge and Hall, 1975).

While the results of surgery for thyrotoxicosis in pregnancy are satisfactory (Talbert et al, 1970; Emslander et al, 1974) many physicians prefer to manage thyrotoxic patients with antithyroid drugs. Methods of employing these agents in pregnancy remain controversial. Some recommend antithyroid drugs combined with thyroxine replacement (Selenkow et al, 1973; Prout, 1975) while others (Hamburger, 1972; Mestman et al, 1974; Tunbridge and Hall, 1975) advise the use of antithyroid drugs alone. The divergence of these views stems largely from inadequate information as to the extent to which thyroid hormones cross the placenta from mother to fetus and vice versa. Results with both methods, properly applied, appear to yield equally good results. No final conclusion was reached in a recent debate on the merits or demerits of combined therapy for thyrotoxicosis in pregnancy (Hamburger, 1972; Selenkow, 1972). Until recently, our preference had been for the combined antithyroid-drug-thyroxine regime which had been used to treat the majority of patients attending the joint antenatal endocrine clinic in the Royal Maternity Hospital, Belfast. The aim was to use the smallest dose of an antithyroid drug to control symptoms after which a supplemental dose of thyroxine (0.1 to 0.2 mg daily) was added to maintain euthyroidism in the mother. Carbimazole has been the drug of choice, and is

given in a dose of 30 mg daily (10 mg eight-hourly) and reduced to 20 mg daily (5 mg six-hourly) or less once control has been achieved. Other suitable drugs are propylthiouracil, PTU (100 mg eight-hourly for more severe cases and 50 mg six-hourly for milder ones) and methimazole (similar to carbimazole). More recently, propylthiouracil has been shown not only to block glandular synthesis of T_4, but also to inhibit the conversion of thyroxine to triiodothyronine extra-thyroidally (Abuid and Larsen, 1974). For this reason, PTU may possess a small advantage over carbimazole which does not exert this extrathyroidal effect.

Propranolol may be given without risk in pregnancy until near term. Normally it is used to control symptoms until the action of antithyroid drugs on hormone synthesis takes effect. Propranolol has been suggested as an alternative to antithyroid drugs (Langer et al, 1974) but its use cannot be recommended as sole therapy in pregnancy, because it is impossible to predict those patients who will respond from those who will not (Lowe et al, 1976). Furthermore, it has been shown that infants of women who were receiving propranolol were more depressed at birth than the babies of those who had received placebo tablets. Propranolol has an extra-thyroidal action and increases the production of rT_3 while lowering the level of triiodothyronine.

Antithyroid drugs cross the placental barrier and if given in excess, may cause an abortion, or hypothyroidism and a goitre in the fetus. Accordingly, they must be given with care, in the *smallest* dose necessary to control the hyperthyroidism and combined with thyroxine (0.1 to 0.2 mg) to maintain the maternal free thyroxine index at a normal level. Where it is possible to monitor the response to treatment with sequential TSH estimations thyroxine replacement can be omitted (Tunbridge and Hall, 1975). Any rise in serum TSH above normal indicates over-treatment and the need to reduce the dose of antithyroid drug. This is now the preferred method of treatment in the Royal Maternity Hospital.

Control of the hyperthyroidism should be assessed on clinical grounds and by serial estimation of the FTI, serum T_4 and T_3 and TSH. If there is to be any deviation from normal, the patient should be allowed to remain slightly hyperthyroid. Once good control is achieved, the rose of the antithyroid drug can usually be reduced with safety for the remainder of the pregnancy. In the majority, if the mother has remained euthyroid or or slightly hyperthyroid, the child will be normal at birth. Rarely, the infant may have exophthalmos, a goitre and congenital thyrotoxicosis. This results from maternal thyroid stimulating immunoglobulins reaching the fetal thyroid via the placenta. Babies born to thyrotoxic mothers should be screened for hyperthyroidism. Mothers of those at greatest risk have pretibial myxoedema and severe apthalmopathy. In mild cases, the condition remits spontaneously after four to six weeks when maternal immunoglobulins are eliminated from the baby's circulation. If symptoms and signs are severe, carbimazole (2.5 mg eight-hourly) is given for a few weeks combined with iodine (Lugol's solution one drop three times daily) or propranolol (2.5 to 8 mg six-hourly) may be used as sole therapy (Pemberton et al, 1974). Antithyroid drugs are excreted in milk, so that babies born to mothers who are receiving them must not be breast fed.

Medical treatment for hyperthyroidism in pregnancy is entirely satisfactory if proper care is taken. In this series of sixty-eight pregnancies treated medically, four babies were lost (5.8 per cent) and there were four infants with goitre and neonatal Graves' disease. In one, the goitre was said to be retrosternal. No infant was hypothyroid. Of the babies that died, two were anencephalics and one had multiple congenital defects. If these are eliminated the corrected total fetal loss was 1.4 per cent. In Table III these results are compared with those obtained by other authors.

TABLE III

Fetal loss in thyrotoxic patients treated in pregnancy Method of treatment and number of pregnancies

Authors		*Surgery*	*Antithyroid drug alone*	*Antithyroid drug and thyroxine supplement*	*Fetal loss (%)*
Herbst and Selenkow	1965	0	0	32	9.4
Bokat	1968	0	41	0	4.7
Enslander et al	1974*	274	0	0	8.0
Mujtaba and Burrow	1975	0	68	0	15.0
Royal Maternity Hospital, Belfast	1979	3	5	63	7.0

* Combined series from the literature.

In the remaining five patients, thyroidectomy was performed in three. Two were untreated because they were seen late in pregnancy.On of these was the first case of T_3 thyrotoxicosis recognized in the Royal Maternity Hospital (Martin et al, 1976).

HYPOTHYROIDISM

Is is rare for patients with significant hypothroidism to conceive (Echt and Doss, 1963), and the incidence of spontaneous abortion and stillbirth is increased (Man et al, 1951). Usually, patients become pregnant after they have been treated for previously diagnosed hypothyroidism.

The clinical features of hypothyroidism are well known but minor degrees may be overlooked because of the physical changes that accompany normal pregnancy. Attention should be focussed on an excessive gain in weight, dry skin, undue fatigue, cold intolerance, pallor not supported by anaemia and delayed relaxation of the ankle jerk. The diagnosis is established by finding an elevated TSH (10 μU/ml or greater), a low T_4, T_3 and FTI. Treatment with thyroxine (0.1 to 0.2 mg daily) must be sufficient to achieve euthyroidism which

is confirmed biochemically by the return of the TSH to normal, a FTI at the upper normal level and a T_3 T_4 and PBI in the normal pregnant range. If a patient diagnosed previously becomes pregnant, replacement treatment is continued and the dose adjusted to ensure adequate suppression of the TSH level. Patients with partial degrees of thyroid insufficiency (subclinical hypothyroidism) picked up by routine assay of TSH (Evered et al, 1973) should receive adequate substitution therapy until the termination of pregnancy, after which thyroid function may be reassessed.

Occasionally, patients with untreated hypothyroidism may conceive and carry their pregnancy successfully to term (Hodges et al, 1952; Echt and Doss, 1963) and their offspring have been reported to be normal. There were two patients with hypothyroidism who gave birth to normal infants in this series (Kennedy and Montgomery, 1978). Temporary amelioration of maternal hypothyroidism as the consequence of fetal thyroid hormone production was observed in one case. In contrast, a number of studies of human hypothyroidism have shown an increased incidence of physical and mental abnormalities in the offspring, in particular, permanent defects in the central nervous system (Man et al, 1958). Man (1972) reported an increased incidence of low mental scores in infants born to inadequately treated "hypothyroxinemic" mothers compared to euthyroid controls. However, the diagnosis of "hypothyroxinaemia", based on a low BEI and clinical features unsupported by other biochemical findings, appears to be insufficient evidence upon which to judge the effect of maternal thyroid hypofunction on the infant's mental development. The subject needs to be restudied using direct hormone assays, in particular TSH, to enable maternal thyroid function to be determined with confidence.

In this series, three of the hypothyroid mothers' babies died (4.6 per cent). Two were premature and death was attributed to prematurity and respiratory distress syndrome. Neither showed any thyroid pathology at postmortem. The other was an intrauterine death at 39 weeks. The fetus had Fallot's tetralogy. The mother had an abnormal GTT at 32 weeks and was classified as a potential diabetic.

NON-TOXIC GOITRE

Enlargement of the thyroid is common in pregnancy (Crooks et al, 1964) but its prevalence varies in different areas and on the clinical criteria adopted for its diagnosis. It is much less in areas of high iodine intake (Crooks et al, 1967). Simple goitres which enlarge in pregnancy probably never return to their non-pregnant size.

The complications of haemorrhage into cysts, hypothyroidism and malignant change should always be borne in mind. Haemorrhage may cause a sudden increase in size of the gland, pain and dyspnoea. The blood-filled cyst may be tender. A thyroid scintiscan is contraindicated in pregnancy but ultrasound is safe and gives information about the nature of a suspicious nodule (Ramsay and Meire, 1975). There is evidence that patients with a goitre in pregnancy may not always be able to maintain euthyroidism, so it is important to assess thyroid

function regularly. Hypothyroidism has to be looked for carefully since signs are mild. Thyroxine must be given if the TSH level rises and the FTI falls below normal. Malignant disease must be considered if the voice is hoarse, if the gland is painful or enlarges rapidly, or if examination shows it to be hard, fixed or associated with enlarged lymph nodes.

The development of a single nodule in the thyroid during pregnancy requires careful assessment. If the nodule is hard, painful or fixed or has enlarged rapidly it should be removed without delay. If none of these features is present it probably is safe to observe the patient or to prescribe suppressive therapy with thyroxine. Further investigation of the lesion with appropriate radioiodine tests can then be undertaken after delivery.

Nodular goitres usually enlarge during pregnancy. Provided normal thyroid function is maintained and there are no obstructive features or other complicating features, treatment of the goitre is unnecessary. Occasionally, patients with congenital biosynthetic errors of thyroid hormone synthesis of mild degree, become pregnant. All of these ultimately interfere with hormone production and cause hypothyroidism and formation of a goitre. They can be effectively treated in pregnancy with thyroxine.

In this series of 59 pregnancies in patients with non-toxic goitre, two babies were lost, an incidence of 3.3 per cent.

CARCINOMA OF THE THYROID

The development of corcinoma of the thyroid during pregnancy is very rare. The main difficulty is to recognize the early case which does not show charactcristic signs. The only safe course is to remain suspicious in every patient with thyroid disease and to consider the possibility of malignancy in every goitre. A nodule, which is apparently single and develops fairly quickly is the most likely presentation and usually denotes a papillary growth. It must be differentiated from a thyroid cyst with or without haemorrhage into it or an area of focal thyroiditis. However, if suspicion of malignancy is high the neck must be explored forthwith. Rapidly expanding tumours of the thyroid which are thought to be carcinomatous must be removed promptly without regard to the pregnancy. A previous history of carcinoma of the thyroid is not a contraindication to pregnancy, nor does the pregnancy adversely affect the prognosis of the cancer (Rosvoll and Winship, 1965). This observation has been amply confirmed in the present series. Most commonly the two conditions are seen together in women who have previously been treated for papillary carcinoma of the thyroid and who are on suppressive thyroxine treatment. They should be watched for signs of recurrence and thyroxine suppression should be continued unaltered. Ten of our patients previously treated for carcinoma (papillary 8, follicular 1, medullary 1) had 13 children without loss between them.

THYROIDITIS

Subacute thyroiditis and chronic lymphotcytic thyroiditis may rarely complicate pregnancy. The former causes painful swelling of the gland which may

be diffuse or focal. Signs of mild hyperthyroidism may follow temporarily. The course is subacute and the fever which is low or moderate, persists for several weeks. Signs in the thyroid usually resolve in two to four months. Occasionally the course is chronic and swelling of the thyroid persists much longer. Eventually, resolution is complete and late sequelae have not been observed. Confirmation of the diagnosis may be difficult because radioactive iodine uptake tests are contraindicated. The ESR is always raised and low titres of thyroid antibodies may be found. These combined with the clinical features and tender thyroid are usually sufficient to suggest the correct diagnosis. Treatment with steroids is highly effective but is usually contraindicated in the first trimester because there may be increased risk of congenital abnormalities (Popert, 1962). Other methods which are probably less effective, are antithyroid drugs (carbimazole 30mg daily for two to three weeks) or suppression with thyroxine. Occasionally, a patient presents with a diffuse or hard enlargement of the thyroid and sometimes features of hypothyroidism. Estimation of the thyroid autoantibodies will confirm the diagnosis of chronic lymphocytic thyroiditis (Hashimoto's thyroiditis). Treatment with thyroxine, whether thyroid function is depressed or not, is necessary and the results are satisfactory. Thyroiditis (Table II) was observed in eight pregnancies in this series. No adverse effect on fetal development was seen.

FETAL RESULTS

Hyperthyroidism in pregnancy has been reported to be associated with a slight increase in perinatal mortality and a significant increase in the frequency of low birth weight babies (Niswander and Gordon, 1972). It is uncertain if there is a real increase in the incidence of congenital abnormalities or if antithyroid drugs could be a contributory factor.

TABLE IV

Thyroid disease in pregnancy. Fetal loss 1963-78.

Disease	*Number*	*Abortions*	*Stillbirth*	*Neonatal death*	*Total fetal loss* (%)	*Perinatal mortality* (%)
Hyperthyroidism	73	1	4	0	5(6.8)	4(5.4)
Hypothyroidism	64	0	1	2	3(4.6)	3(4.6)
Non-toxic goitre	59	0	2	0	2(3.3)	2(3.3)
Miscellaneous group	112	1	4	1	6(5.3)	5(4.4)
Total	308	2	11	3	16(5.1)	14(4.5)

311 fetuses – 3 sets of twins

Table IV shows fetal loss for the whole series. The hyperthyroid group had the highest total fetal loss and perinatal mortality, but allowing for the small numbers involved there is really not much difference between the groups. During the period under review the hospital perinatal mortality varied between 65.44 per 1,000 in 1963 and 20.46 per 1,000 in 1977 and the same steady downward trend was observed in all the thyroid groups studied. Only the hyperthyroid and miscellaneous groups come near the maximum hospital perinatal mortality rate. Both these, however, and indeed the other groups were heavily weighed with congenital abnormalities and complications unlikely to be connected with thyroid disease (Table V).

TABLE V

Causes of fetal death in thyroid disease in pregnancy unlikely to be related to thyroid disease

Group	*Cause of fetal death*	
Hyperthyroidism	Anencephaly	2
	Multiple congenital defects	1
Hypothyroidism	Fallot's tetralogy with stillbirth	1
Non-toxic goitre	Multiple congenital defects Trisomy D	1
Miscellaneous group	Anencephaly	1
	Severe Rhesus isoimmunization	1
Total		7

In the hyperthyroid group there were two anencephalics and one infant with multiple congenital defects, while in the miscellaneous group there was one anencephalic and one case of severe Rhesus isoimmunization. If these are eliminated the perinatal mortality for the hyperthyroid group becomes 1.3 per cent and for the miscellaneous group 2.6 per cent, while for all groups it is 2.2 per cent. On balance, therefore, there is no evidence to suggest that thyroid disease contributes adversely to the outcome of pregnancy. Furthermore, there was no evidence to support the view that thyrotoxic mothers produce babies of low birth weight. The mean birth weight of the last 14 babies born to treated thyrotoxic mothers in this series was 3170 g.

None of the 311 infants was hypothyroid. Goitres were observed in four babies born to mothers with treated hyperthyroidism and all had neonatal Graves' disease. One mother, with severe Graves' disease and a very high titre of thyroid stimulating immunoglobulins, gave birth to two affected babies in successive pregnancies. Both infants responded well to treatment with propranolol.

The current view that antithyroid drug treatment has no ill effects on fetal development has not gone unchallenged and some of the workers have expressed concern about possible adverse effects of antithyroid drugs on the development

of the central nervous system of the fetus. In Europe, for example, it is customary to give oral contraceptives to women receiving antithyroid medication for hyperthyroidism. Recently, McCarroll et al (1976) investigated 25 children born to women treated with carbimazole in the years 1960 to 1971 inclusive and assessed their growth and psychological and intellectual development against carefully matched controls born in the same week in hospital. It was apparent that the use of carbimazole in pregnancy had no injurious effects on subsequent growth and intellectual development of the children. Greenman et al (1962) and Burrow et al (1968) came to similar conclusions after investigating the use of propylthiouracil in pregnancy. These results, therefore, lend no support to the view that antithyroid drug treatment in pregnancy is harmful for the mental or physical development of the fetus.

SUMMARY

Changes in thyroid function in pregnancy and the nature of thyroid disease seen in the Royal Maternity Hospital, Belfast, over a 16-year period, are reviewed. All patients with a goitre or a previous history of thyroid disease need careful assessment of thyroid function. If there is any departure from normal they need appropriate treatment and careful follow-up for the remainder of the pregnancy. Therapeutic measures available for the treatment of hyperthyroidism are discussed. Antithyroid drugs may be given without risk to the developing fetus.

Contrary to popular belief, hypothyroid patients can conceive and deliver healthy infants without treatment. The phenomenon of amelioration of the mother's hypothyroidism during pregnancy as the result of transplacental passage of fetal thyroid hormone to the mother is noted. It is considered that thyroid disease in pregnancy, provided that it is recognized and correctly treated, does not adversely affect the outcome of the pregnancy.

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