THYROTOXICOSIS IN PREGNANCY

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Thyroid function is closely interrelated with the development and function of the female genital organs. Myxoedema and cretinism delay the onset of menstruation and the development of secondary sexual characteristics. When menstruation is present it tends to be irregular and infrequent. In adult hypothyroidism menorrhagia may occur, while with hyperthyroidism oligomenorrhoea or amenorrhoea frequently occur but menorrhagia is rare. The thyroid gland is affected by changes in reproductive function. Thyroid enlargement is six times as frequent in the postadolescent woman as in man. It is apt to occur at puberty, in pregnancy and at the menopause. Oestrogens are known to affect numerous parameters of thyroid function. Probably owing to an increase in thyroid binding globulin (TBG) the protein bound iodine (PBI) is raised and the radioactive triodothyronin ($^{131}T_3$) red cell or resin uptake is decreased .This fact is of major clinical importance as the contraceptive pill or other oestrogen therapy may cause errors of judgement in the evaluation of thyroid function tests in cases of suspected throid dysfunction.

Fertility is also affected by changes in thyroid function. Sterility is common in myxoedema although instances of pregnancy in severe untreated hypothyroidism have been reported. When pregnancy results, abortion and stillbirths are common. Even when the pregnancy is carried successfully to term, congenital goitre may occur. Moreover a high incidence of developmental abnormalities is seen in euthyroid offspring of hypothryoid mothers. Untreated thyrotoxicosis is also associated with a decreased fertility rate. Keynes (1952) reported a fertility rate of 52.5% in thyrotoxic women before operation compared with a normal rate of 70%.

Thyrotoxicosis is a disease of unknown aetiology with a striking genetic or familial incidence. The condition affects women more often than men and is predominantly a disease of the childbearing era. In spite of this it is rarely found in association with pregnancy. The incidence in reported series varies widely. Silver (1965) comparing the incidence of several series found that the overall mean incidence of thyrotoxicosis in pregnancy is 0.047%.

Before considering the treatment of thyrotoxicosis in pregnancy it is important to determine what effect thyrotoxicosis has on pregnancy, the changes in thyroid function that occur in normal pregnancy and the effect of pregnancy on thyrotoxicosis.

Effect of Thyrotoxicosis on Pregnancy

There is general agreement that uncontrolled thyrotoxicosis predisposes to

abortion, premature delivery and stillbirth and that the risks are proportionate to the severity of the thyrotoxicosis. Proper control eliminates most of these risks as is seen in most modern series. In the past the incidence of pre-eclampsia seems to have been very high in pregnancy complicated by thyrotoxicosis. McLaughin and McGoogen (1943) reported an incidence of 62% in their series of only 19 cases. In contradistinction in Hawe and Francis' series of 70 patients only 4 (5.7%) developed pre-eclampsia. With modern treatment this complication does not occur more commonly than in euthyroid pregnant women.

The foetus is not usually affected by thyrotoxicosis, but rare cases of congenital thyrotoxicosis or exophthalmos have been reported. The condition is usually benign and settles spontaneously or with minimal treatment.

Effect of pregnancy on thyroid function

Most of the symptoms and signs associated with hyperthyroidism are present in a lesser or greater degree in pregnancy.

Many clinical features are common to pregnancy and to thyrotoxicosis. These include increased cardiac action, accelerated peripheral circulation, and decreased heat tolerance. The thyroid gland often enlarges during pregnancy. This was recognised by the ancient Egyptians who used it as a test for pregnancy by tying the stem of a plant round a woman's neck. Pregnancy caused the stem to break. Few well controlled trials into the incidence of goitre in pregnancy have been reported. Crook *et al.* (1964) reporting from Aberdeen found an incidence of 70% in pregnant women against an incidence of 37% in non--pregnant controls. They also noted that the incidence was constant throughout pregnancy.

There are very few reports on the histological changes in the thyroid gland during normal pregnancy. Stoffler (1957) studied the thyroid glands of 65 pregnant women at autopsy and reviewed a further 28 cases from the literature. He found no evidence of increased thyroid weight and suggested that any increase in size must be due to hyperaemia. The histological picture of enlarged follicles full of thin colloid with vacuolisation and an epithelium which is generally hypertrophic led him to conclude that there is increased activity of the thyroid gland during pregnancy.

The basal metabolic rate is increased during pregnancy. The rise is apparent after the fourth or fifth month and gradually rises until term when it is raised about 20% above non-pregnant levels. Attemps to correlate this phenomenon with changes have failed.

TABLE I

Determination	*Non-pregnant normal*	*Pregnant normal*
PBI	4.0–7.5 μg%	6.5–11.5 μg%
BEI	3.2–6.5 μg%	5.5–10.5 μg%
T_3 RBC uptake	11–17%	< 10%
T_3 Resin uptake	25–30%	< 10%
Free thyroxine factor	0.384 (±0.0843)	0.375 (±0.103)
Free thyroxine	1.4–2.5 mμg%	1.4–2.5 mμg%

Normal values for thyroid function tests in pregnancy.

The increased oxygen uptake in pregnancy is probably due to an increase in protoplasmic mass and the increased cardiac and respiratory work which occurs during pregnancy.

PBI also rises early in pregnancy to levels consistent with hyperthyroid states. Increased levels are found as early as 3 to 6 weeks of gestation. Man (1961) reported that the levels are consistently raised by the 16th week of pregnancy. Butanol extractable iodine (BEI) which reflects the total serum thyroxine level shows a similar increase in the binding capacity of the TBG either due to a quantitative increase in the protein or due to a qualitative alteration in its binding capacity. This increase in binding capacity is reflected by a decrease uptake of $^{131}T_3$ by red cells or resin which is seen as early as the fourth week of pregnancy. It is believed that the increase in thyroxine binding capacity, which accounts for the rise in PBI and BEI, is secondary to the effects of oestrogens. However, recent reports do not confirm this.

Radioactive I^{132} which has a half life of only 77 hours has been used to study thyroid activity during pregnancy. Halnan (1958) found that there is an increased uptake of iodine by the thyroid gland during pregnancy. In a later more extensive study by Aboul-Khair (1964), the plasma inorganic I level was found to be low throughout pregnancy. This is due to an increased renal clearance of I which is high throughout pregnancy. This causes a relative iodine deficiency in the immediate vicinity of the thyroid gland with the result that clearance of I by the thyroid is increased in order to maintain the absolute iodine uptake within euthyroid limits. These findings suggest that in normal pregnancy there occurs no increase in thyroid hormone production.

Recent advances in methods available for studying thyroid function have confirmed that normal pregnant women are euthyroid. Free thyroxine factor, which is based on a calculation between $^{131}T_3$ RBC or resin uptake of PBI levels and reflects the level of free thyroxine in the serum, shows no significant difference between normal pregnant and non-pregnant women. Free thyroxine estimations have also been performed and confirm these results. It seems therefore, that the usual tests of thyroid function are distorted by the metabolic and cardiovascular changes which occur during pregnancy and that any enlargement of the thyroid gland is due to the relative iodine deficiency.

These metabolic and cardiovascular changes make the diagnosis of thyrotoxicosis during pregnancy difficult. As we have seen before, certain clinical features of pregnancy and thyrotoxicosis are remarkably similar. However, the more marked these clinical features, the more likely is the probability of co-existing thyrotoxicosis, especially a persistently high sleeping pulse rate, failure to gain weight despite good appetite, excessive sweating, tremor, and a considerably enlarged pulsatile thyroid gland. The presence of exophthalmos may provide valuable evidence as does a history of symptoms which preceded the onset of pregnancy. Laboratory aids are not usually helpful especially in mild cases. The use of I^{131} is contraindicated, but I^{132} may be useful in exceptional circumstances. Halman calculated that with a dose of 6 μc of I^{132} the foetal thyroid is exposed to only 0.01 to 0.06 rads. and the foetal and maternal gonads to less than 0.001 rads. $^{131}T_3$ uptake studies and especially the calculation of free thyroxine factor appear to reflect the true state of thyroid function and may prove to be the best guide as to the severity of the thyrotoxicosis and to the level of control during treatment.

Effects of pregnancy on thyrotoxicosis

Thyrotoxicosis often shows spontaneous changes in severity and this makes interpretation of the effect of pregnancy difficult to evaluate. There is no general agreement, the camp being equally divided between those who consider that adverse effects may occur and those who maintain that pregnancy has a favourable effect on thyrotoxicosis. However, as Hawe and Francis remark there is an increased risk of thyroid crisis during or immediately after delivery.

Treatment of thyrotoxicosis during pregnancy

During pregnancy two plans of treatment are available for the control of thyrotoxicosis. One is to control the hyperthyroidism with antithyroid drugs throughout pregnancy. The alternative is to perform subtotal thyroidectomy after controlling the disease with a short course of antithyroid drugs or iodine. Radioactive iodine which is the method of choice in patients over 45 years of age, is absolutely contraindicated during pregnancy. The isotope crosses the placental barrier and is accumulated with great avidity by the foetal thyroid after the first trimester. The risk of damage to the foetus is very real especially as the thyroid glands of infants are known to be unusually sensitive to radioiodine. Russell *et al.* (1957) reported two cases of severe hypothyroidism in infants whose mothers were given I^{131} during the 13th week of pregnancy.

Medical treatment

Control of thyrotoxicosis with antithyroid drugs throughout the pregnancy is usually considered as the treatment of choice. The dosage varies from patient to patient. The general aim is to obtain control of the hyperthyroid state and then reduce the dose to the minimal maintenance level. In judging the level of control one must always be aware of the apparently raised levels of thyroid function characteristic of normal pregnancy. The usual difficulties of controlling hyperthyroidism are enhanced during pregnancy. Over-treatment may endanger the foetus and under-treatment may lead to an exacerbation of maternal thyrotoxicosis; both situations are associated with an increased risk of foetal loss. In the interests of the foetus the usual practice is to reduce or stop antithyroid drugs during the latter months of pregnancy. Unfortunately due to occasional unexpected early relapses this is not always possible.

Antithyroid drugs are known to cross the placental barrier and depress the foetal thyroid gland. This results in increased production of thyroid stimulating hormone (TSH) and hyperplasia of the foetal gland. Foetal goitre is usually transient and subsides spontaneously; however, several instances of a large goitre leading to neonatal death from tracheal compression have been recorded and several cretins have resulted from the use of antithyroid drugs. Furthermore, antithyroid drugs are excreted in the milk and therefore breast feeding is contraindicated during their use.

In spite of these difficulties some excellent series have been reported. Astwood (1951) treated 19 patients with propylthiouracil or Carbimazole, substantially reducing the dosage during the second half of pregnancy. He obtained 22 live infants from 22 pregnancies and no foetal goitres. Piper and Rosen (1954) following a similar regime recorded four abortions and one stillbirth among 16 pregnancies. They reviewed the literature and were able to find records of 83 pregnancies during which antithyroid drugs were used to control hyperthyroidism, with a foetal loss of 6. Of the 77 viable infants 14 had goitres. Similar difficulties were experienced by Becker and Suddith (1959) and Hawe and Francis (1962). However, Herbert (1965) reported a series of 32 pregnancies during which antithyroid drugs were used following the usual regime, adding USP thyroid 120-180 mg. when the thyrotoxicosis was under control. They reported a foetal loss of only three and no instance of foetal goitre. The addition of thyroid hormone may be useful in avoiding maternal hypothyroidism, but it is doubtful what beneficial effects this has on the foetus as thyroxine crosses the placental barrier very slowly (Myant 1958).

Table II summarises the results of several series where antithyroid drugs were used to control thyrotoxicosis in pregnancy. Out of a total of 245 pregnancies, the foetal loss was 33 (13.5%); two of these were neonatal deaths due to a suffocative goitre. Of the 212 live infants 23 had goitres and 2 were cretins, an incidence of goitre of 9%.

Surgery

Subtotal thyroidectomy has been performed for the control of thyrotoxicosis

TABLE II

Author	*No. pregs.*	*Foetal loss*	*Viable infants*	*No. goitres*
Series prior to 1954 according to Piper and Rosen	83	6	77	15
Piper and Rosen (1954)	16	5	11	0
Becker and Suddith (1959)	34	9	25	2 1 cretin
Hawe and Frances (1962)	39	5	34	1 cretin
Burrow (1965)	41	5	36	5
Herbst (1965)	32	3	29	0
TOTAL	245	33 (13.5%)	212	24 (9%)

Foetal loss and incidence of goitre in series treated by antithyroid drugs.

during pregnancy since the beginning of this century. Almost consistently good results have been obtained. The operation is usually performed during the 2nd trimester due to the possibility of causing miscarriage if it is performed earlier. Even when performed during the first trimester instances of miscarriage following operation are rare. Prior to the introduction of the antithyroid drugs patients were prepared with iodine. Piper and Rosen (1954) collected 122 cases from the literature with a foetal loss of four. No foetal abnormalities occurred.

More recently antithyroid drugs have been used to obtain control of the hyperthyroidism as subtotal thyroidectomy is safer if performed on euthyroid patients. Lugol's iodine is given for 1-2 weeks prior to operation in order to diminish the increased vascularity of the thyroid gland which results from the use of antithyroid drugs. Following this regime most authors report good results. Bell and Hall (1960) suggest that the use of thyroid replacement therapy following operation is worthwhile as results seem to be greatly improved. They treated 21 pregnant patients with subtotal thyroidectomy following antithyroid drug therapy. In this group of patients there were 4 abortions and 1 stillbirth. Following this experience they treated a further 21 pregnant patients with a similar regime, but prescribed dessicated thyroid post-operatively until term. Only one infant, a stillbirth, was lost. Other authors (Hawe and Francis) have not confirmed this advantage of thyroid replacement therapy, but its use is justified as hypothyroidism may occur after surgery.

Table III summarises the results of several series where thyrotoxicosis was treated by subtotal thyroidectomy during pregnancy following control with iodine alone or with antithyroid drugs. Out of 300 pregnancies the foetal loss was only 22 (7.3%). No goitres occurred. Only one infant, a mongol, showed congenital abnormalities.

TABLE III

Author	*No. Pregs.*	*Foetal loss*	*Viable infants*
Collected series according to Piper and Rosen (1954)	122	4	118
Dailey and Benson (1952)	17	3	14
Stoffler (1957)	21	3	18
Holt (1959)	3	0	3
Becker and Suddith (1959)	8	1	7
Bell and Hall (1960)	42	6	36
Lange (1961)	31	1	30
Hawe (1965)	38	2	36
Hamilton (1968)	18	2	16
TOTAL	300	22 (7.3%)	278

Foetal loss in series treated with subtotal thyroidectomy.

Discussion

These figures provide good evidence of the safety of subtotal thyroidectomy for the mother and child. Occasional maternal deaths have occurred following surgery (Stoffler 1959), but maternal deaths have also been recorded with medical treatment (Hawe and Francis 1962). Although the numbers are small and not suitable for statistical analysis the rate of foetal loss and of neonatal mortality and morbidity are generally lower and more consistent following surgery, than with antithyroid drugs. It appears that operation during pregnancy does not increase the risk or adversely affect the foetus and, therefore, most of the pros and cons which affect the choice of treatment in young non-pregnant patients are valid during pregnancy.

At present the choice of treatment is largely determined by whether the patient is referred to a surgeon or a physician. Most physicians regard medical treatment as the method of choice in pregnancy (Crooke and Wayne 1960). With good medical care it is possible to obtain good results (Astwood 1951, Herbst 1965), but from time to time difficulties arise which may be outside the control of the clinician especially as treatment involves a compromise between the interests of the mother and of the foetus. Moreover the recurrence rate requiring subtotal thyroidectomy, following delivery, is high, (Piper and Rosen 1954, Becker and Suddith 1959, Hawe and Francis 1962).

Subtotal thyroidectomy does not have many of these disadvantages. Following operation the patient quickly returns to a euthyroid state, the pregnancy will then proceed as in any normal patient and breast feeding is not restricted. Moreover the recurrence rate after operation is low and subsequent pregnancies are not complicated by the persistence of the hyperthyroid state. There are certain qualifications which have to be fulfilled prior to undertaking surgery. The diagnosis, of course, must be assured; this avoids unne-

cessary operations on the mildly toxic patient in whom the diagnosis in pregnancy may be very difficult and who might recover spontaneously. The patient must be seen early in pregnancy as otherwise not enough time is available to make the patient euthyroid before operation. No contraindications to operation must be present.

In the final analysis the medical and surgical facilities available and the special circumstances of each individual patient will determine the management of a particular case. However, subtotal thyroidectomy performed by experienced surgeons appears to offer better prospects to the foetus and the mother.

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